

SUBSTITUTED THIOACETAMIDES

REFERENCE TO RELATED APPLICATIONS

The present application claims priority to U.S. Provisional application Serial No. 60/204,789, filed May 16, 2000 and U.S. provisional application Serial No. 60/268,283, 5 filed February 13, 2001. The disclosure of each of these applications is hereby incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

The present invention is related to chemical compositions, processes for the preparation thereof and uses of the composition. Particularly, the present invention 10 relates to compositions that include substituted thioacetamides, and their use in the treatment of diseases, including treatment of sleepiness, promotion of wakefulness, treatment of Parkinson's disease, cerebral ischemia, stroke, sleep apneas, eating disorders, stimulation of appetite and weight gain, treatment of attention deficit hyperactivity disorder ("ADHD"), enhancing function in disorders associated with 15 hypofunctionality of the cerebral cortex, including, but not limited to, depression, schizophrenia, fatigue, in particular, fatigue associated with neurologic disease, such as multiple sclerosis, chronic fatigue syndrome, and improvement of cognitive dysfunction.

BACKGROUND OF THE INVENTION

The compounds disclosed herein are related to the biological and chemical 20 analogs of modafinil. Modafinil, $C_{15}H_{15}NO_2S$, also known as 2-(benzhydrylsulfinyl) acetamide, or 2-[(diphenylmethyl) sulfinyl] acetamide, is a synthetic acetamide derivative with wake-promoting activity, the structure of which has been described in French Patent No. 78 05 510 and in U.S. Patent No. 4,177,290 ('290), and which has been approved by the United States Food and Drug Administration for use in the 25 treatment of excessive daytime sleepiness associated with narcolepsy. Modafinil has been tested for treatment of several behavioral conditions in combination with various

agents including apomorphine, amphetamine, reserpine, oxotremorine, hypnotics, yohimbine, 5-hydroxytryptophan, and monoamine oxidase inhibitors, as described in the cited patents. A method of preparation of a racemic mixture is described in the '290 patent and a method of preparation of a levorotatory isomer is described in U.S. Patent 5 No. 4,927,855 (both incorporated herein by reference). The levorotatory isomer is reported to be useful for treatment of hypersomnia, depression, Alzheimer's disease and to have activity towards the symptoms of dementia and loss of memory, especially in the elderly.

The primary pharmacological activity of modafinil is to promote wakefulness. 10 Modafinil promotes wakefulness in rats (Touret et al., 1995; Edgar and Seidel, 1997), cats (Lin et al., 1992), canines (Shelton et al., 1995) and non-human primates (Hernant et al, 1991) as well as in models mimicking clinical situations, such as sleep apnea (English bulldog sleep disordered breathing model) (Panckeri et al, 1996) and narcolepsy (narcoleptic canine) (Shelton et al, 1995). 15 Modafinil has also been described as an agent with activity in the central nervous system, and as a useful agent in the treatment of Parkinson's disease (U.S. Patent No. 5,180,745); in the protection of cerebral tissue from ischemia (U.S. Patent No. 5,391,576); in the treatment of urinary and fecal incontinence (U.S. Patent No. 5,401,776); and in the treatment of sleep apneas and disorders of central origin (U.S. 20 Patent No. 5,612,379). U.S. Patent No. 5,618,845 describes modafinil preparations of a defined particle size less than about 200 microns. In addition, modafinil may be used in the treatment of eating disorders, or to promote weight gain or stimulate appetite in humans or animals (US Provisional Patent Application No. 60/150,071, incorporated herein by reference), or in the treatment of attention deficit hyperactivity disorder 25 (ADHD), or fatigue, especially fatigue associated with multiple sclerosis (US Provisional Patent Application No. 60/149,612, incorporated herein by reference).

Several published patent applications describe derivative forms of modafinil and the use of modafinil derivatives in the treatment of various disorders. For example, PCT publication WO 99/25329 describes analogs of modafinil in which the phenyl groups are 30 substituted with a F, Cl, Br, CF₃, NO₂, NH₂, C₁-C₄ alkyl, C₁-C₄ alkoxy, or methylenedioxy, and in which the amide is substituted with OH, C₁-C₄ alkyl, C₁-C₄ hydroxylalkyl, or a C₁-C₄ hydrocarbon radical. These compositions are described as

being useful for treating drug-induced sleepiness, especially sleepiness associated with administration of morphine to cancer patients.

Similarly, U.S. Pat. No. 4,066,686 describes benzhydrylsulphinyl derivatives, including modafinil derivatives with an extended alkyl chain between the sulfinyl and carbonyl groups and where NR_3R_4 is NHOH. These compounds are described as being useful in therapy for treating disturbances of the central nervous system.

PCT publication WO 95/01333 describes modafinil derivatives that are useful for modifying feeding behavior. The modifications to modafinil described include a chloro group at the 3 position of one of the phenyl groups, and a pyridyl substituted for the 10 second phenyl, substitution of one or two methyl groups for hydrogens at the 2-carbon position, the amide hydrogens may be substituted with one or two groups selected from H, a pyridyl-methyl or ethyl groups, and further where the sulfur may not be oxidized.

PCT publication WO 95/01171 also describes modified modafinil compounds that are said to be useful for modifying eating behavior. The described compounds 15 include substitutions of 4-fluoro-, 3-fluoro-, and 4 chloro- in a first phenyl group and 4-fluoro- or 3-fluoro- substitutions in the second phenyl. Also described are substitutions in which the amide contains substitutions with an OH or isopropyl group.

Terauchi, H, et al. described nicotinamide derivatives useful as ATP-ase inhibitors (Terauchi, H, et al, *J. Med. Chem.*, 1997, 40, 313-321). In particular, several 20 N-alkyl substituted 2-(Benzhydrylsulfinyl) nicotinamides are described.

U.S. Pat. Nos. 4,980,372 and 4,935,240 describe benzoylaminophenoxybutanoic acid derivatives. In particular, sulfide derivatives of modafinil containing a phenyl and substituted phenyl linker between the sulfide and carbonyl, and a substituted aryl in the terminal amide position, are disclosed.

25 Other modafinil derivatives have been disclosed wherein the terminal phenyl groups are constrained by a linking group. For example, in U.S. Pat. No. 5,563,169, certain xanthenyl and thianthenyl derivatives having a substituted aryl in the terminal amide position are reported.

Other xanthenyl and thianthenyl derivatives are disclosed in Annis, I; Barany, 30 *G. Pept. Proc. Am. Pept. Symp. 15th* (Meeting Date 1997) 343-344, 1999 (preparation of a xanthenyl derivative of Ellman's Reagent, useful as a reagent in peptide synthesis); Han, Y.; Barany, G. *J. Org. Chem.*, 1997, 62, 3841-3848 (preparation of S-xanthenyl

protected cysteine derivatives, useful as a reagent in peptide synthesis); and El-Sakka, I.A., et al. *Arch. Pharm. (Weinheim)*, 1994, 327, 133-135 (thiaxanthenol derivatives of thioglycolic acid).

Thus, there is a need for novel classes of compounds that possess beneficial properties. It has been discovered that a class of compounds, referred to herein as substituted thioacetamides, are useful as agents for treating or preventing diseases or disorders, including treatment of sleepiness, promotion of wakefulness, treatment of Parkinson's disease, cerebral ischemia, stroke, sleep apneas, eating disorders, stimulation of appetite and weight gain, treatment of attention deficit hyperactivity disorder, enhancing function in disorders associated with hypofunctionality of the cerebral cortex, including, but not limited to, depression, schizophrenia, fatigue, in particular, fatigue associated with neurologic disease, such as multiple sclerosis, chronic fatigue syndrome, and improvement of cognitive dysfunction. The present invention is directed to these, as well as other, important ends.

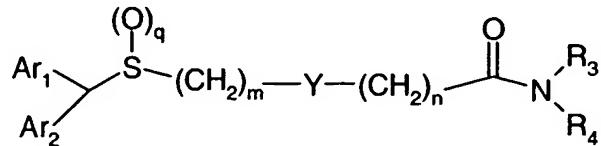
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SUMMARY OF THE INVENTION

One aspect of the present invention provides, in part, various novel substituted thioacetamides. Other aspects of the invention also include their pharmaceutical compositions, methods of their preparation, and use of the compounds in the treatment of diseases.

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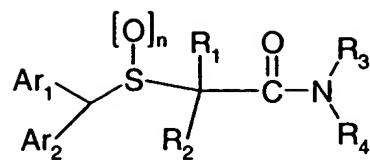
In one aspect of the invention, there are provided compounds of formula (I-A):



(I-A)

Constituent members and preferred embodiments are disclosed in detail *infra*.

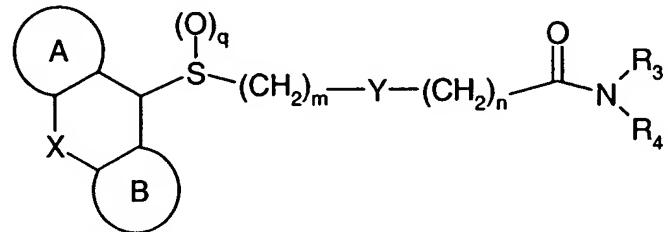
In another aspect of the invention, there are provided compounds of formula (I):



(I)

Constituent members and preferred embodiments are disclosed in detail *infra*.

Another object of the present invention is to provide compounds of formula (II-A):

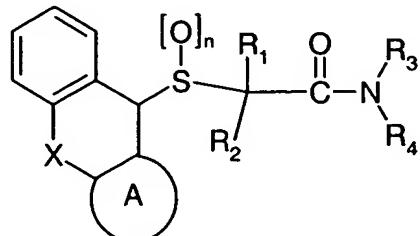


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(II-A)

Constituent members and preferred embodiments are disclosed in detail *infra*.

An additional object of the present invention is to provide compounds of formula (II):



(II)

10 Constituent members and preferred embodiments are disclosed in detail *infra*.

Another object of the present invention is to provide methods of treating or preventing diseases or disorders, including treatment of sleepiness, promotion of wakefulness, treatment of Parkinson's disease, cerebral ischemia, stroke, sleep apneas,

5 eating disorders, stimulation of appetite and weight gain, treatment of attention deficit hyperactivity disorder, enhancing function in disorders associated with hypofunctionality of the cerebral cortex, including, but not limited to, depression, schizophrenia, fatigue, in particular, fatigue associated with neurologic disease, such as multiple sclerosis, chronic fatigue syndrome, and improvement of cognitive dysfunction.

10 Another object of the present invention is to provide pharmaceutical compositions comprising the compounds of the present invention wherein the compositions comprise one or more pharmaceutically acceptable excipients and a therapeutically effective amount of at least one of the compounds of the present invention, or a pharmaceutically acceptable salt or ester form thereof.

15 These and other objects, features and advantages of the substituted thioacetamides will be disclosed in the following detailed description of the patent disclosure.

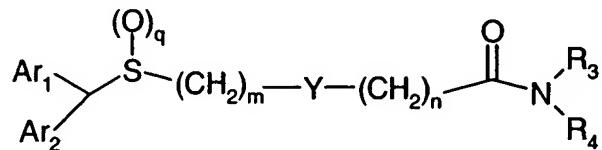
BRIEF DESCRIPTION OF THE DRAWINGS

15 FIG. 1 is a graph of data indicating EEG-determined wakefulness in rats treated with Compound I-9 (100 mg/kg, ip; solid line) or methylcellulose vehicle (stippled line). Wakefulness is quantified in 5-minute bins. N= 13 rats/group. *p<0.05 vs. vehicle treated animals.

20 FIG. 2 is a graph of data indicating EEG-determined wakefulness in rats treated with compound II-23 (100 mg/kg, ip; solid triangles) or methylcellulose vehicle (open circles). Each point represents the mean percent of time awake for the succeeding half hour. *p<0.05 vs. vehicle treated animals.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the present invention provides novel compounds of formula (I-A):



(I-A)

wherein:

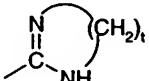
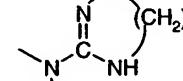
5 Ar_1 and Ar_2 are each independently selected from $\text{C}_6\text{-C}_{10}$ aryl or heteroaryl;
 wherein each of Ar_1 or Ar_2 may be independently optionally substituted with 1-3
 substituents independently selected from:

a) H , $\text{C}_6\text{-C}_{10}$ aryl, heteroaryl, F , Cl , Br , I , $-\text{CN}$, $-\text{CF}_3$, $-\text{NO}_2$, $-\text{OH}$, $-\text{OR}_7$, $-\text{O}(\text{CH}_2)_p\text{NR}_9\text{R}_{10}$, $-\text{OC}(\text{=O})\text{R}_7$, $-\text{OC}(\text{=O})\text{NR}_9\text{R}_{10}$, $-\text{O}(\text{CH}_2)_p\text{OR}_8$, $-\text{CH}_2\text{OR}_8$,
 $-\text{NR}_9\text{R}_{10}$, $-\text{NR}_8\text{S}(\text{=O})_2\text{R}_7$, $-\text{NR}_8\text{C}(\text{=O})\text{R}_7$, or $-\text{NR}_8\text{C}(\text{=S})\text{R}_7$;

b) $-\text{CH}_2\text{OR}_{11}$;

c) $-\text{NR}_8\text{C}(\text{=O})\text{NR}_9\text{R}_{10}$, $-\text{NR}_8\text{C}(\text{=S})\text{NR}_9\text{R}_{10}$, $-\text{CO}_2\text{R}_{12}$, $-\text{C}(\text{=O})\text{R}_{13}$, $-\text{C}(\text{=O})\text{NR}_9\text{R}_{10}$, $-\text{C}(\text{=S})\text{NR}_9\text{R}_{10}$, $-\text{CH}=\text{NOR}_{12}$, $-\text{CH}=\text{NR}_7$, $-(\text{CH}_2)_p\text{NR}_9\text{R}_{10}$, $-(\text{CH}_2)_p\text{NHR}_{11}$, $-\text{CH}=\text{NNR}_{12}\text{R}_{12A}$, $-\text{C}(\text{=NR}_8)\text{NR}_8\text{A}\text{R}_{8B}$, $-\text{NR}_8\text{C}(\text{=NH})\text{R}_{8A}$, $-\text{NR}_8\text{C}(\text{=NH})\text{NR}_8\text{A}\text{R}_{8B}$,

or


;


d) $-\text{S}(\text{O})_y\text{R}_7$, $-(\text{CH}_2)_p\text{S}(\text{O})_y\text{R}_7$, $-\text{CH}_2\text{S}(\text{O})_y\text{R}_7$; and

e) $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_2\text{-C}_8$ alkenyl, or $\text{C}_2\text{-C}_8$ alkynyl, where:

1) each alkyl, alkenyl, or alkynyl group is unsubstituted; or

2) each alkyl, alkenyl or alkynyl group is independently substituted
 with 1 to 3 groups independently selected from $\text{C}_6\text{-C}_{10}$ aryl,
 heteroaryl, F , Cl , Br , I , CF_3 , $-\text{CN}$, $-\text{NO}_2$, $-\text{OH}$, $-\text{OR}_7$, $-\text{CH}_2\text{OR}_8$, $-\text{NR}_9\text{R}_{10}$, $-\text{O}-(\text{CH}_2)_p\text{-OH}$, $-\text{S}-(\text{CH}_2)_p\text{-OH}$, $-\text{X}_1(\text{CH}_2)_p\text{OR}_7$,

X₁(CH₂)_pNR₉R₁₀, -X₁(CH₂)_pC(=O)NR₉R₁₀, -
X₁(CH₂)_pC(=S)NR₉R₁₀, -X₁(CH₂)_pOC(=O)NR₉R₁₀, -
X₁(CH₂)_pCO₂R₈, -X₁(CH₂)_pS(O)_yR₇, -X₁(CH₂)_pNR₈C(=O)NR₉R₁₀,
-C(=O)R₁₃, -CO₂R₁₂, -OC(=O)R₇, -C(=O)NR₉R₁₀, -
OC(=O)NR₁₂R_{12A}, O-tetrahydropyranyl, -C(=S)NR₉R₁₀, -
CH=NNR₁₂R_{12A}, -CH=NOR₁₂, -CH=NR₇, -
CH=NNHCH(N=NH)NH₂, -NR₈CO₂R₇, -NR₈C(=O)NR₉R₁₀, -
NR₈C(=S)NR₉R₁₀, -NHC(=NH)NH₂, -NR₈C(=O)R₇, -
NR₈C(=S)R₇, -NR₈S(=O)₂R₇, -S(O)_yR₇, -S(=O)₂NR₁₂R_{12A}, -
P(=O)(OR₈)₂, -OR₁₁, and a C₅-C₇ monosaccharide where each
hydroxyl group of the monosaccharide is independently either
unsubstituted or is replaced by H, C₁-C₄ alkyl, C₁-C₄ alkoxy, or -
O-C(=O)R₇;

X₁ is -O-, -S-, -N(R₈)-;

5 15 Y is selected from C₁-C₄ alkylene, C₆-C₁₀ arylene, heteroarylene, C₃-C₈ cycloalkylene,
heterocyclene, -O-, -N(R₈)-, -S(O)_y, -CR_{8A}=CR_{8B}-, -CH=CH-CH(R₈)-, -
CH(R₈)-CH=CH-, or -C≡C-; with the proviso that when Y is -O-, -N(R₈)-, or -
S(O)_y, m and n cannot be 0; R₃ and R₄ are the same or different and are each
selected from H, C₁-C₆ alkyl, -OH, and -CH(R₆)-CONR_{8A}R_{8B}, provided that R₃
and R₄ are not both OH; or R₃ and R₄, together with the nitrogen to which they
are attached, form a 3-7 member heterocyclic ring;

10 20 R₃ and R₄ are the same or different and are each selected from H, C₁-C₆ alkyl, -OH, and -
CH(R₆)-CONR_{8A}R_{8B}, provided that R₃ and R₄ are not both OH; or R₃ and R₄,
together with the nitrogen to which they are attached, form a 3-7 member
heterocyclic ring;

25 R₆ is H, C₁-C₄ alkyl or the side chain of an α -amino acid;
R₇ is C₁-C₆ alkyl, C₆-C₁₀ aryl, or heteroaryl;
R₈, R_{8A} and R_{8B} are each independently H, C₁-C₄ alkyl, or C₆-C₁₀ aryl;
R₉ and R₁₀ are independently selected from H, C₁-C₄ alkyl, and C₆-C₁₀ aryl; or R₉ and
30 R₁₀ together with the nitrogen to which they are attached, form a 3-7 member
heterocyclic ring;

R_{11} is the residue of an amino acid after the hydroxyl group of the carboxyl group is removed;

R_{12} and R_{12A} are each independently selected from H, C₁-C₆ alkyl, cycloalkyl, C₆-C₁₀ aryl, and heteroaryl; or R_{12} and R_{12A} , together with the nitrogen to which they are attached, form a 5-7 member heterocyclic ring;

R_{13} is H, C₁-C₆ alkyl, cycloalkyl, C₆-C₁₀ aryl, heteroaryl, -C(=O)R₇, -C(=O)NR₉R₁₀, or -C(=S)NR₉R₁₀;

m is 0, 1, 2 or 3;

n is 0, 1, 2 or 3;

10 p is from 1, 2, 3, or 4;

q is 0, 1, or 2;

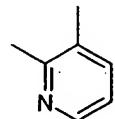
t is 2, 3, or 4;

y is 0, 1 or 2;

with the proviso that when Ar_1 is phenyl and Ar_2 is phenyl or pyridyl, then Y cannot be

15 C₁-C₄ alkylene;

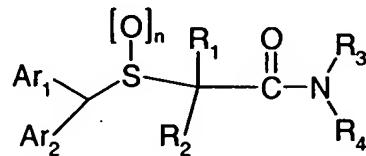
with the further proviso that when Ar_1 and Ar_2 are phenyl, q=1, m and n = 0, Y is



, and R_3 is H, then R_4 is not C₁-C₆ alkyl;

and the stereoisomeric forms, mixtures of stereoisomeric forms, or pharmaceutically acceptable salt and ester forms thereof.

20 In an additional embodiment of the invention, there are provided compounds of formula (I):



(I)

wherein Ar₁ and Ar₂ are the same or different and are each selected from thiophene, isothiazole, phenyl, pyridyl, oxazole, isoxazole, thiazole, imidazole, and other five or six membered heterocycles comprising 1-3 atoms of -N-, -O-, or -S-, provided that Ar₁ and Ar₂ are not both phenyl and when Ar₁ is phenyl, Ar₂ is not pyridyl; R₁-R₄ are the same or different and are each selected from H, lower alkyl, -OH, -CH(R₆)-CONR_{6A}R_{6B}, or any of R₁-R₄ can be taken together to form a 3-7 member carbocyclic or heterocyclic ring, provided that R₃ and R₄ are not both OH; R_{6A} and R_{6B} are independently H or lower alkyl; and n is 0, 1, or 2; and in addition, each of Ar₁ or Ar₂ may be independently optionally substituted with one or more substituents independently selected from:

- a) H, aryl, heterocycll, F, Cl, Br, I, -CN, -CF₃, -NO₂, -OH, -OR₇, -O(CH₂)_pNR₉R₁₀, -OC(=O)R₇, -OC(=O)NR₉R₁₀, -O(CH₂)_pOR₈, -CH₂OR₈, -NR₉R₁₀, -NR₈S(=O)₂R₇, -NR₈C(=O)R₇, or -NR₈C(=S)R₇;
- b) -CH₂OR₁₁, where R₁₁ is the residue of an amino acid after the hydroxyl group of the carboxyl group is removed;
- c) -NR₈C(=O)NR₉R₁₀, -NR₈C(=S)NR₉R₁₀, -CO₂R₁₂, -C(=O)R₁₂, -C(=O)NR₉R₁₀, -C(=S)NR₉R₁₀, -CH=NOR₁₂, -CH=NR₇, -(CH₂)_pNR₉R₁₀, -(CH₂)_pNHR₁₁, or -CH=NNR₁₂R_{12A}, where R₁₂ and R_{12A} are the same or different and each are independently selected from H, alkyl of 1 to 4 carbons, -OH, alkoxy of 1 to 4 carbons, -OC(=O)R₇, -OC(=O)NR₉R₁₀, -OC(=S)NR₉R₁₀, -O(CH₂)_pNR₉R₁₀, -O(CH₂)_pOR₈, substituted or unsubstituted arylalkyl having from 6 to 10 carbons, and substituted or unsubstituted heterocyclalkyl;
- d) -S(O)_yR₁₂, -(CH₂)_pS(O)_yR₇, -CH₂S(O)_yR₁₁ where y is 0, 1 or 2; and
- e) alkyl of 1 to 8 carbons, alkenyl of 2 to 8 carbons, or alkynyl of 2 to 8 carbons, where:
 - 1) each alkyl, alkenyl, or alkynyl group is unsubstituted; or
 - 2) each alkyl, alkenyl or alkynyl group is substituted with 1 to 3 groups selected from aryl of 6 to 10 carbons, heterocycll, arylalkoxy, heterocycloalkoxy, hydroxylalkoxy, alkyloxy-alkoxy, hydroxyalkylthio, alkoxy-alkylthio, F, Cl, Br, I, -CN, -NO₂, -OH, -OR₇, -X₂(CH₂)_pNR₉R₁₀, -X₂(CH₂)_pC(=O)NR₉R₁₀, -

X₂(CH₂)_pC(=S)NR₉R₁₀, -X₂(CH₂)_pOC(=O)NR₉R₁₀, -
X₂(CH₂)_pCO₂R₇, -X₂(CH₂)_pS(O)_yR₇, -X₂(CH₂)_pNR₈C(=O)NR₉R₁₀, -
-OC(=O)R₇, -OC(=O)NHR₁₂, O-tetrahydropyranyl, -NR₉R₁₀, -
NR₈CO₂R₇, -NR₈C(=O)NR₉R₁₀, -NR₈C(=S)NR₉R₁₀, -
NHC(=NH)NH₂, -NR₈C(=O)R₇, -NR₈C(=S)R₇, -NR₈S(=O)₂R₇, -
S(O)_yR₇, -CO₂R₁₂, -C(=O)NR₉R₁₀, -C(=S)NR₉R₁₀, -C(=O)R₁₂, -
CH₂OR₈, -CH=NNR₁₂R_{12A}, -CH=NOR₁₂, -CH=NR₇, -
CH=NNHCH(N=NH)NH₂, -S(=O)₂NR₁₂R_{12A}, -P(=O)(OR₈)₂, -
OR₁₁, and a monosaccharide of 5 to 7 carbons where each
5 hydroxyl group of the monosaccharide is independently either
unsubstituted or is replaced by H, alkyl of 1 to 4 carbons,
alkylcarbonyloxy of 2 to 5 carbons, or alkoxy of 1 to 4 carbons,
where X₂ is O, S, or NR₈; where
R₇ is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or
10 substituted or unsubstituted heterocyclyl;
R₈ is H or alkyl having from 1 to 4 carbons;
p is from 1 to 4; and where either
15 1) R₉ and R₁₀ are each independently H, unsubstituted alkyl of 1 to 4
carbons, or substituted alkyl; or
20 2) R₉ and R₁₀ together form a linking group of the formula -(CH₂)₂-
X₁-(CH₂)₂, wherein X₁ is selected from -O-, -S-, and -CH₂-;
and the stereoisomeric forms, mixtures of stereoisomeric forms, or pharmaceutically
acceptable salt and ester forms thereof.
In a preferred embodiment of the invention, there are provided compounds of
25 formula (I) wherein Ar₁ and Ar₂ are the same or different and are each selected from
thiophene, isothiazole, phenyl, oxazole, isoxazole, thiazole, imidazole, or other five or
six membered heterocycles comprising 1-3 atoms of -N-, -O-, or -S-, provided that Ar₁
and Ar₂ are not both phenyl; R₁-R₄ are the same or different and are each selected from
H, lower alkyl, -OH, -CH(R₆)-CONR_{6A}R_{6B}, or any of R₁-R₄ can be taken together to
30 form a 3-7 member carbocyclic or heterocyclic ring, provided that R₃ and R₄ are not both
OH; R_{6A} and R_{6B} are independently H or lower alkyl; and n is 0, 1, or 2; and in addition,

each of Ar₁ or Ar₂ may be independently optionally substituted with one or more substituents independently selected from:

- a) H, aryl, heterocyclyl, F, Cl, Br, I, -CN, -CF₃, -NO₂, -OH, -OR₇, -O(CH₂)_pNR₉R₁₀, -OC(=O)R₇, -OC(=O)NR₉R₁₀, -O(CH₂)_pOR₈, -CH₂OR₈, -NR₉R₁₀, -NR₈S(=O)₂R₇, -NR₈C(=O)R₇, or -NR₈C(=S)R₇;
- 5 b) -CH₂OR₁₁, where R₁₁ is the residue of an amino acid after the hydroxyl group of the carboxyl group is removed;
- c) -NR₈C(=O)NR₉R₁₀, -NR₈C(=S)NR₉R₁₀, -CO₂R₁₂, -C(=O)R₁₂, -C(=O)NR₉R₁₀, -C(=S)NR₉R₁₀, -CH=NOR₁₂, -CH=NR₇, -(CH₂)_pNR₉R₁₀, -
10 (CH₂)_pNHR₁₁, or -CH=NNR₁₂R_{12A}, where R₁₂ and R_{12A} are the same or different and each are independently selected from H, alkyl of 1 to 4 carbons, -OH, alkoxy of 1 to 4 carbons, -OC(=O)R₇, -OC(=O)NR₉R₁₀, -OC(=S)NR₉R₁₀, -O(CH₂)_pNR₉R₁₀, -O(CH₂)_pOR₈, substituted or unsubstituted arylalkyl having from 6 to 10 carbons, and substituted or unsubstituted heterocyclylalkyl;
- 15 d) -S(O)_yR₁₂, -(CH₂)_pS(O)_yR₇, -CH₂S(O)_yR₁₁ where y is 0, 1 or 2; and
- e) alkyl of 1 to 8 carbons, alkenyl of 2 to 8 carbons, or alkynyl of 2 to 8 carbons, where:
 - 1) each alkyl, alkenyl, or alkynyl group is unsubstituted; or
 - 20 2) each alkyl, alkenyl or alkynyl group is substituted with 1 to 3 groups selected from aryl of 6 to 10 carbons, heterocyclyl, arylalkoxy, heterocycloalkoxy, hydroxylalkoxy, alkyloxy-alkoxy, hydroxylalkylthio, alkoxy-alkylthio, F, Cl, Br, I, -CN, -NO₂, -OH, -OR₇, -X₂(CH₂)_pNR₉R₁₀, -X₂(CH₂)_pC(=O)NR₉R₁₀, -
25 X₂(CH₂)_pC(=S)NR₉R₁₀, -X₂(CH₂)_pOC(=O)NR₉R₁₀, -X₂(CH₂)_pCO₂R₇, -X₂(CH₂)_pS(O)_yR₇, -X₂(CH₂)_pNR₈C(=O)NR₉R₁₀, -OC(=O)R₇, -OC(=O)NHR₁₂, O-tetrahydropyranyl, -NR₉R₁₀, -NR₈CO₂R₇, -NR₈C(=O)NR₉R₁₀, -NR₈C(=S)NR₉R₁₀, -NHC(=NH)NH₂, -NR₈C(=O)R₇, -NR₈C(=S)R₇, -NR₈S(=O)₂R₇, -
30 S(O)_yR₇, -CO₂R₁₂, -C(=O)NR₉R₁₀, -C(=S)NR₉R₁₀, -C(=O)R₁₂, -CH₂OR₈, -CH=NNR₁₂R_{12A}, -CH=NOR₁₂, -CH=NR₇, -CH=NNHCH(N=NH)NH₂, -S(=O)₂NR₁₂R_{12A}, -P(=O)(OR₈)₂, -

OR₁₁, and a monosaccharide of 5 to 7 carbons where each hydroxyl group of the monosaccharide is independently either unsubstituted or is replaced by H, alkyl of 1 to 4 carbons, alkylcarbonyloxy of 2 to 5 carbons, or alkoxy of 1 to 4 carbons, where X₂ is O, S, or NR₈; where

5

R₇ is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heterocycl;

R₈ is H or alkyl having from 1 to 4 carbons;

p is from 1 to 4; and where either

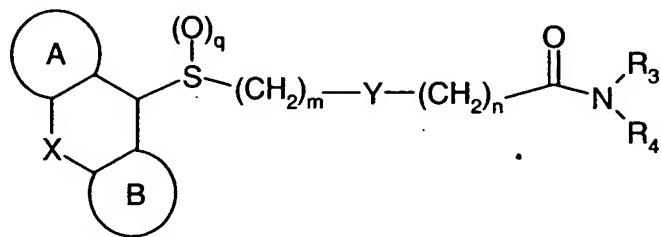
10 1) R₉ and R₁₀ are each independently H, unsubstituted alkyl of 1 to 4 carbons, or substituted alkyl; or

2) R₉ and R₁₀ together form a linking group of the formula -(CH₂)₂-X₁-(CH₂)₂-, wherein X₁ is selected from -O-, -S-, and -CH₂-;

and the stereoisomeric forms, mixtures of stereoisomeric forms, or pharmaceutically

15 acceptable salt and ester forms thereof.

In another embodiment of the invention, there is provided novel compounds of the formula (II-A):



(II-A)

wherein

20 X is a bond, -CH₂CH₂-, -O-, -S(O)_y-, -N(R₈)-, -CHN(R₈)-, -CH=CH-, -CH₂-CH=CH-, C(=O), -C(R₈)=N-, -N=C(R₈)-, -C(=O)-N(R₈)-, or -NR₈-C(=O)-;

Rings A and B, together with the carbon atoms to which they are attached, are each independently selected from:

25 a) a 6-membered aromatic carbocyclic ring in which from 1 to 3 carbon atoms may be replaced by hetero atoms selected from oxygen, nitrogen and sulfur; and

b) a 5-membered aromatic carbocyclic ring in which either:

- i) one carbon atom is replaced with an oxygen, nitrogen, or sulfur atom;
- ii) two carbon atoms are replaced with a sulfur and a nitrogen atom, an oxygen and a nitrogen atom, or two nitrogen atoms; or
- iii) three carbon atoms are replaced with three nitrogen atoms, one oxygen and two nitrogen atoms, or one sulfur and two nitrogen atoms;

5

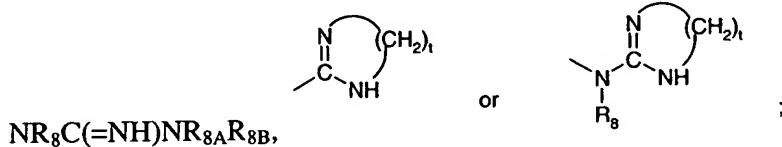
wherein Ring A and Ring B may each independently be substituted with 1-3 substituents

10

selected from:

15

- a) H, C₆-C₁₀ aryl, heteroaryl, F, Cl, Br, I, -CN, -CF₃, -NO₂, -OH, -OR₇, -O(CH₂)_pNR₉R₁₀, -OC(=O)R₇, -OC(=O)NR₉R₁₀, -O(CH₂)_pOR₈, -CH₂OR₈, -NR₉R₁₀, -NR₈S(=O)₂R₇, -NR₈C(=O)R₇, or -NR₈C(=S)R₇;
- b) -CH₂OR₁₁;
- c) -NR₈C(=O)NR₉R₁₀, -NR₈C(=S)NR₉R₁₀, -CO₂R₁₂, -C(=O)R₁₃, -C(=O)NR₉R₁₀, -C(=S)NR₉R₁₀, -CH=NOR₁₂, -CH=NR₇, -(CH₂)_pNR₉R₁₀, -(CH₂)_pNHR₁₁, -CH=NNR₁₂R_{12A}, -C(=NR₈)NR_{8A}R_{8B} -NR₈C(=NH)R_{8A}, -



20

- e) C₁-C₈ alkyl, C₂-C₈ alkenyl, or C₂-C₈ alkynyl, where:

25

- 1) each alkyl, alkenyl, or alkynyl group is unsubstituted; or
- 2) each alkyl, alkenyl or alkynyl group is independently substituted with 1 to 3 groups independently selected from C₆-C₁₀ aryl, heteroaryl, F, Cl, Br, I, CF₃, -CN, -NO₂, -OH, -OR₇, -CH₂OR₈, -NR₉R₁₀, -O-(CH₂)_p-OH, -S-(CH₂)_p-OH, -X₁(CH₂)_pOR₇, X₁(CH₂)_pNR₉R₁₀, -X₁(CH₂)_pC(=O)NR₉R₁₀, -X₁(CH₂)_pC(=S)NR₉R₁₀, -X₁(CH₂)_pOC(=O)NR₉R₁₀, -X₁(CH₂)_pCO₂R₈, -X₁(CH₂)_pS(O)_yR₇, -X₁(CH₂)_pNR₈C(=O)NR₉R₁₀, -C(=O)R₁₃, -CO₂R₁₂, -OC(=O)R₇, -C(=O)NR₉R₁₀, -OC(=O)NR₁₂R_{12A}, O-tetrahydropyranyl, -C(=S)NR₉R₁₀, -

30

CH=NNR₁₂R_{12A}, -CH=NOR₁₂, -CH=NR₇, -
CH=NNHCH(N=NH)NH₂, -NR₈CO₂R₇, -NR₈C(=O)NR₉R₁₀, -
NR₈C(=S)NR₉R₁₀, -NHC(=NH)NH₂, -NR₈C(=O)R₇, -
NR₈C(=S)R₇, -NR₈S(=O)₂R₇, -S(O)_yR₇, -S(=O)₂NR₁₂R_{12A}, -
P(=O)(OR₈)₂, -OR₁₁, and a C₅-C₇ monosaccharide where each
5 hydroxyl group of the monosaccharide is independently either
unsubstituted or is replaced by H, C₁-C₄ alkyl, C₁-C₄ alkoxy, or -
O-C(=O)R₇; R₃ and R₄ are the same or different and are each
selected from H, C₁-C₆ alkyl, -OH, -CH(R₆)-CONR_{8A}R_{8B},
10 provided that R₃ and R₄ are not both OH, or R₃ and R₄, together
with the nitrogen to which they are attached, form a 3-7 member
heterocyclic ring;

R₃ and R₄ are the same or different and are each selected from H, C₁-C₆ alkyl, -OH, and -
CH(R₆)-CONR_{8A}R_{8B}, provided that R₃ and R₄ are not both OH; or R₃ and R₄,
15 together with the nitrogen to which they are attached, form a 3-7 member
heterocyclic ring;

R₆ is H, C₁-C₄ alkyl or the side chain of an α -amino acid;

R₇ is C₁-C₆ alkyl, C₆-C₁₀ aryl, or heteroaryl;

R₈, R_{8A} and R_{8B} are each independently H, C₁-C₄ alkyl, or C₆-C₁₀ aryl;

20 R₉ and R₁₀ are independently selected from H, C₁-C₄ alkyl, and C₆-C₁₀ aryl; or R₉ and
R₁₀ together with the nitrogen to which they are attached, form a 3-7 member
heterocyclic ring;

R₁₁ is the residue of an amino acid after the hydroxyl group of the carboxyl group is
removed;

25 R₁₂ and R_{12A} are each independently selected from H, C₁-C₆ alkyl, cycloalkyl, C₆-C₁₀
aryl, and heteroaryl; or R₁₂ and R_{12A}, together with the nitrogen to which they are
attached, form a 5-7 member heterocyclic ring;

R₁₃ is H, C₁-C₆ alkyl, cycloalkyl, C₆-C₁₀ aryl, heteroaryl, -C(=O)R₇, -C(=O)NR₉R₁₀, or -
C(=S)NR₉R₁₀;

30 X₁ is -O-, -S-, -N(R₈)-;
Y is selected from C₁-C₄ alkylene, C₆-C₁₀ arylene, heteroarylene, C₃-C₈ cycloalkylene,
heterocyclylene, -O-, -N(R₈)-, -S(O)_y, -CR_{8A}=CR_{8B}-, -CH=CH-CH(R₈)-, -

CH(R₈)-CH=CH-, or -C≡C-; with the proviso that when Y is -O-, -N(R₈)-, or -S(O)_y, m and n cannot be 0;

m is 0, 1, 2 or 3;

n is 0, 1, 2 or 3;

5 p is from 1 to 4;

q is 0, 1, 2;

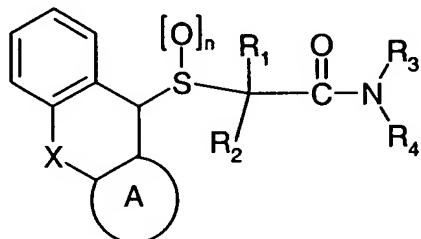
t is 2, 3, or 4;

y is 0, 1 or 2;

and the stereoisomeric forms, mixtures of stereoisomeric forms, or pharmaceutically

10 acceptable salt and ester forms thereof.

In a further embodiment, there are provided compounds of formula (II):



(II)

where X is -(CH₂)_m-, -O-, -S(O)_n-, -N(R₅)-, -CH=CH-, or -CH₂-CH=CH-; m is 0,

1, 2 or 3; n is 0, 1 or 2; R₁-R₄ are the same or different and are each selected from H,

15 lower alkyl, -OH, -CH(R₆)-CONR₇R₈, or any of R₁-R₄ can be taken together to form a 3-7 member carbocyclic or heterocyclic ring; R₅ is H, lower alkyl, or -OH; R₆, R₇ and R₈ is H or lower alkyl; and ring A, together with the carbon atoms to which it is attached is selected from:

a) a 6-membered carbocyclic ring in which from 1 to 3 carbon atoms may be

20 replaced by hetero atoms selected from oxygen, nitrogen and sulfur; and

b) a 5-membered carbocyclic ring in which either:

i) one carbon atom may be replaced with an oxygen, nitrogen, or sulfur

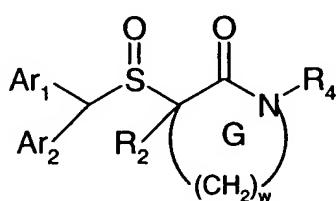
atom;

ii) two carbon atoms may be replaced with a sulfur and a nitrogen atom, an oxygen and a nitrogen atom, or two nitrogen atoms; or
iii) three carbon atoms may be replaced with three nitrogen atoms, one oxygen and two nitrogen atoms, or one sulfur and two nitrogen atoms;

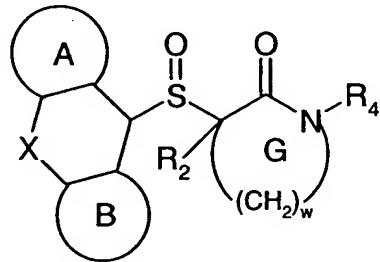
5 and the stereoisomeric forms, mixtures of stereoisomeric forms, or pharmaceutically acceptable salt and ester forms thereof.

As with any group of structurally related compounds which possess a particular utility, certain groups and configurations are preferred for the compounds of the present invention in their end-use application.

10 In some embodiments of formula (I-A) or (II-A), Y= -C(R₁)(R₂), wherein R₁ and R₂ are each independently selected from H or C₁-C₆ alkyl; and optionally, either R₁ or R₂ can combine with either R₃ or R₄ to form a 5-7 membered heterocyclic ring. In some particular embodiments, R₁ combines with R₃ to form compounds (III) and (IV):



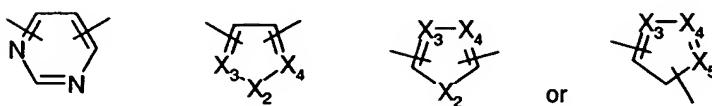
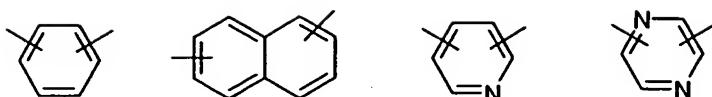
(III)



(IV)

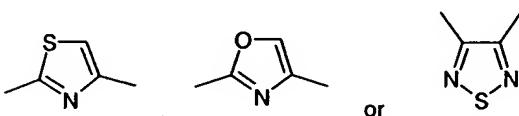
15 wherein w is 2, 3, or 4.

In certain embodiments of formula (I-A), Ar₁ and Ar₂ are each independently selected from a five or six membered heteroaryl comprising 1-3 atoms of -N-, -O-, or -S-. Preferably, q=1. In preferred embodiments, Ar₁ and Ar₂ are each independently selected from thienyl, isothiazolyl, pyridyl, oxazolyl, isoxazolyl, thiazolyl, and imidazolyl, and more preferably, Ar₁ and Ar₂ are thienyl, and particularly Ar₁ and Ar₂ are 3-thienyl. In other preferred embodiments, Y is -O-, -S(O)_y-, or -N(R₈)-. In another preferred embodiment, Y is C₁-C₄ alkylene. In an additional embodiment, Y is -CR_{8A}=CR_{8B}-, -CH=CH-CH(R₈)-, -CH(R₈)-CH=CH-, or -C≡C-. In certain preferred embodiments, Y is C₆-C₁₀ arylene or heteroarylene, and preferably, m=0 or 1 and n=0 or 1. More preferably, Y is

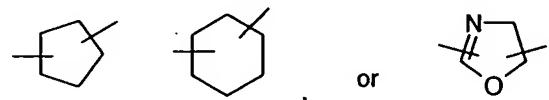


wherein X_2 is $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}(\text{O})_y-$, or $-\text{N}(\text{R}_8)-$; and X_3 , X_4 , and X_5 are each independently selected from $-\text{CH}-$, or $-\text{N}-$. Most preferably, Y is phenylene. In another more preferred embodiment, Y is

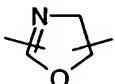
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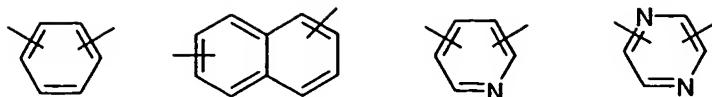
In yet another embodiment, Y is furanylene. In further preferred embodiments, Y is $\text{C}_3\text{-C}_8$ cycloalkylene or heterocyclylene. Preferably, Y is



or

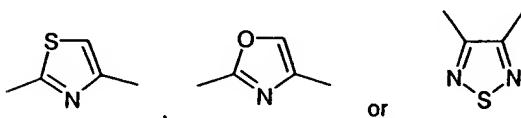


In other embodiments of formula (I-A), Ar_1 is phenyl and Ar_2 is a five or six membered heteroaryl comprising 1-3 atoms of $-\text{N}-$, $-\text{O}-$, or $-\text{S}-$. Preferably, $q=1$. In other preferred embodiments, Ar_1 and Ar_2 are each independently phenyl, thienyl, isothiazolyl, pyridyl, oxazolyl, isoxazolyl, thiazolyl, and imidazolyl. In further preferred embodiments, Ar_1 is phenyl and Ar_2 is thienyl, isothiazolyl, pyridyl, oxazolyl, isoxazolyl, thiazolyl, and imidazolyl, and more preferably, Ar_1 is phenyl and Ar_2 is thienyl, and particularly, Ar_2 is 3-thienyl. In other preferred embodiments, Y is $-\text{O}-$, $-\text{S}(\text{O})_y-$, or $-\text{N}(\text{R}_8)-$. In another preferred embodiment, Y is $\text{C}_1\text{-C}_4$ alkylene. In an additional embodiment, Y is $-\text{CR}_{8A}=\text{CR}_{8B}-$, $-\text{CH}=\text{CH}-\text{CH}(\text{R}_8)-$, $-\text{CH}(\text{R}_8)-\text{CH}=\text{CH}-$, or $-\text{C}\equiv\text{C}-$. In certain preferred embodiments, Y is $\text{C}_6\text{-C}_{10}$ arylene or heteroarylene, and preferably, $m=0$ or 1 and $n=0$ or 1 . More preferably, Y is

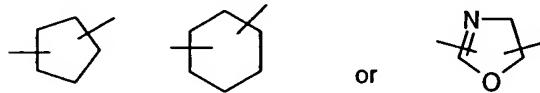


wherein X_2 is $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}(\text{O})_y-$, or $-\text{N}(\text{R}_8)-$; and X_3 , X_4 , and X_5 are each independently selected from $-\text{CH}-$, or $-\text{N}-$. Most preferably, Y is phenylene. In another more preferred embodiment, Y is

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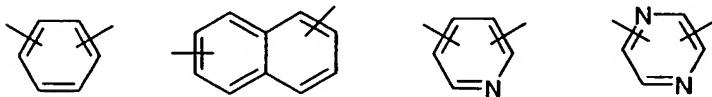


In yet another embodiment, Y is furanylene. In further preferred embodiments, Y is $\text{C}_3\text{-C}_8$ cycloalkylene or heterocyclylene. Preferably, Y is



In another embodiment of formula (I-A), Ar_1 and Ar_2 is phenyl. Preferably, $q=1$.

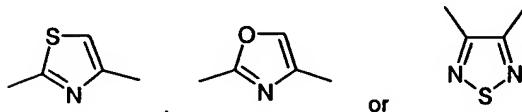
10 In other preferred embodiments, Y is $-\text{O}-$, $-\text{S}(\text{O})_y-$, or $-\text{N}(\text{R}_8)-$. In another preferred embodiment, Y is $\text{C}_1\text{-C}_4$ alkylene. In an additional embodiment, Y is $-\text{CR}_{8A}=\text{CR}_{8B}-$, $-\text{CH}=\text{CH}-\text{CH}(\text{R}_8)-$, $-\text{CH}(\text{R}_8)-\text{CH}=\text{CH}-$, or $-\text{C}=\text{C}-$. In certain preferred embodiments, Y is $\text{C}_6\text{-C}_{10}$ arylene or heteroarylene, and preferably, $m=0$ or 1 and $n=0$ or 1. More preferably, Y is



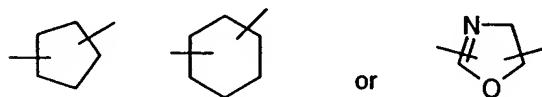
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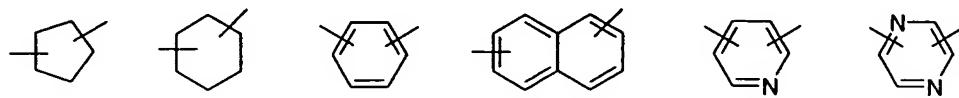
wherein X_2 is $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}(\text{O})_y-$, or $-\text{N}(\text{R}_8)-$; and X_3 , X_4 , and X_5 are each independently selected from $-\text{CH}-$, or $-\text{N}-$. Most preferably, Y is phenylene. In another more preferred embodiment, Y is



5 In yet another embodiment, Y is furanylene. In further preferred embodiments, Y is $\text{C}_3\text{-C}_8$ cycloalkylene or heterocyclylene. Preferably, Y is

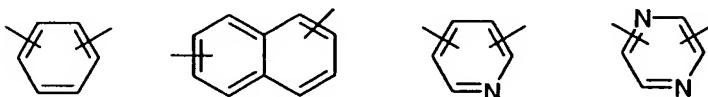


In an additional embodiment of formula (I-A), Y is $-\text{O}-$, $-\text{S}(\text{O})_y-$, $-\text{N}(\text{R}_8)-$, $\text{C}_1\text{-C}_4$ alkylene, $-\text{CR}_{8A}=\text{CR}_{8B}-$, $-\text{CH}=\text{CH}-\text{CH}(\text{R}_8)-$, $-\text{CH}(\text{R}_8)-\text{CH}=\text{CH}-$, $-\text{C}\equiv\text{C}-$,

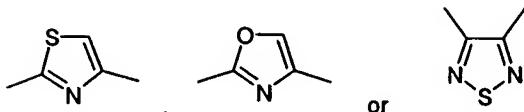


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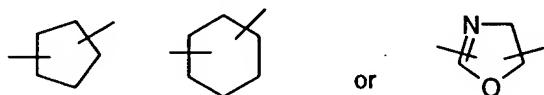
wherein X_2 is $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}(\text{O})_y-$, or $-\text{N}(\text{R}_8)-$; and X_3 , X_4 , and X_5 are each independently selected from $-\text{CH}-$, or $-\text{N}-$. In other preferred embodiments, Y is $-\text{O}-$, $-\text{S}(\text{O})_y-$, or $-\text{N}(\text{R}_8)-$. In another preferred embodiment, Y is $\text{C}_1\text{-C}_4$ alkylene. In an additional embodiment, Y is $-\text{CR}_{8A}=\text{CR}_{8B}-$, $-\text{CH}=\text{CH}-\text{CH}(\text{R}_8)-$, $-\text{CH}(\text{R}_8)-\text{CH}=\text{CH}-$, or $-\text{C}\equiv\text{C}-$. In certain preferred embodiments, Y is $\text{C}_6\text{-C}_{10}$ arylene or heteroarylene, and preferably, $m=0$ or 1 and $n=0$ or 1 . More preferably, Y is



wherein X_2 is $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}(\text{O})_y-$, or $-\text{N}(\text{R}_8)-$; and X_3 , X_4 , and X_5 are each independently selected from $-\text{CH}-$, or $-\text{N}-$. Most preferably, Y is phenylene. In another more preferred embodiment, Y is



5 In yet another embodiment, Y is furanylene. In further preferred embodiments, Y is $\text{C}_3\text{-C}_8$ cycloalkylene or heterocyclylene. Preferably, Y is

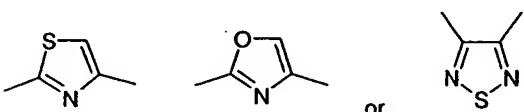


In yet another embodiment of formula (I-A), $q=1$.

In a further embodiment of formula (I-A), Ar_1 and Ar_2 are each independently selected from phenyl and thienyl, and $q=1$. Preferably Ar_1 and Ar_2 are each independently selected from phenyl and 3-thienyl, and $q=1$. In other preferred embodiments, Y is $-\text{O}-$, $-\text{S}(\text{O})_y-$, or $-\text{N}(\text{R}_8)-$. In another preferred embodiment, Y is $\text{C}_1\text{-C}_4$ alkylene. In an additional embodiment, Y is $-\text{CR}_{8A}=\text{CR}_{8B}-$, $-\text{CH}=\text{CH}-\text{CH}(\text{R}_8)-$, $-\text{CH}(\text{R}_8)-\text{CH}=\text{CH}-$, or $-\text{C}\equiv\text{C}-$. In certain preferred embodiments, Y is $\text{C}_6\text{-C}_{10}$ arylene or heteroarylene, and preferably, $m=0$ or 1 and $n=0$ or 1. More preferably, Y is



wherein X_2 is $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}(\text{O})_y-$, or $-\text{N}(\text{R}_8)-$; and X_3 , X_4 , and X_5 are each independently selected from $-\text{CH}-$, or $-\text{N}-$. Most preferably, Y is phenylene. In another more preferred embodiment, Y is



In yet another embodiment, Y is furanylene. In further preferred embodiments, Y is C₃-C₈ cycloalkylene or heterocyclylene. Preferably, Y is



, or

Preferred embodiments of formula (I-A) are compounds wherein Ar₁ and Ar₂ are
5 the same or different and are each selected from thiophene, isothiazole, phenyl, pyridyl,
oxazole, isoxazole, thiazole, imidazole, provided that Ar₁ and Ar₂ are both not phenyl
and when Ar₁ is phenyl, Ar₂ is not pyridyl.

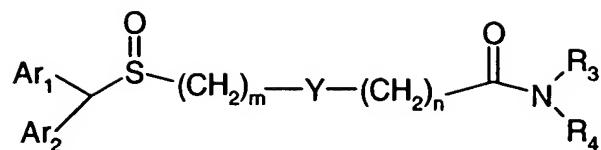
Preferred embodiments of formula (I) are compounds wherein Ar₁ and Ar₂ are
the same or different and are each selected from thiophene, isothiazole, phenyl, oxazole,
10 isoxazole, thiazole, imidazole, provided that Ar₁ and Ar₂ are both not phenyl. Other
preferred embodiments are those where Ar₁ and Ar₂ are each independently substituted.

Additional preferred embodiments of formula (I) are given below:

- 1) Compounds in which Ar₁, Ar₂ or both are thiophene;
- 2) Compounds in which Ar₁, Ar₂ or both are isothiazole;
- 15 3) Compounds in which Ar₁, Ar₂ or both are pyridyl;
- 4) Compounds in which Ar₁, Ar₂ or both are oxazole;
- 5) Compounds in which Ar₁, Ar₂ or both are isoxazole;
- 6) Compounds in which Ar₁, Ar₂ or both are thiazole;
- 7) Compounds in which Ar₁, Ar₂ or both are imidazole,
- 20 8) Compounds in which Ar₁ is phenyl and Ar₂ is thiophene.

In a preferred embodiment of the of formula (I-A), there are provided compounds
as represented in Table 1:

Table 1



No.	Ar ₁	Ar ₂	Y	m	n	NR ₃ R ₄
I-1	3-Thienyl	3-Thienyl	-CH ₂ -	1	0	NH ₂
I-2	3-Thienyl	3-Thienyl	-CH ₂ -	1	0	NMe ₂
I-3	3-Thienyl	3-Thienyl	-CH ₂ -	2	1	NH ₂
I-4	3-Thienyl	3-Thienyl	-CH ₂ -	1	0	NHCH(CH ₃)- CONH ₂
I-5	3-Thienyl	3-Thienyl	-C(CH ₃) ₂ -	1	0	NH ₂
I-6	3-Thienyl	3-Thienyl		1	0	NH ₂
I-7	Ph	3-Thienyl		1	0	NH ₂
I-8	Ph	3-Thienyl	-CH ₂ -	2	1	NH ₂
I-9	3-Thienyl	3-Thienyl	-CH ₂ -	0	0	NH ₂
I-10	3-Thienyl	3-Thienyl	-CH ₂ -	0	0	NH(C ₃ H ₇)
I-11	3-Thienyl	3-Thienyl	-CH ₂ -	0	0	N(CH ₃) ₂
I-12	3-Thienyl	3-Thienyl	-CH ₂ -	0	0	N(CH ₂ CH ₃) ₂
I-13	3-Thienyl	3-Thienyl	-CH ₂ -	0	0	morpholino
I-14	3- Isothiazolyl	3- Isothiazolyl	-CH ₂ -	0	0	NH ₂
I-15	4-Thiazolyl	4-Thiazolyl	-CH ₂ -	0	0	NH ₂
I-16	2-Thiazolyl	2-Thiazolyl	-CH ₂ -	0	0	NH ₂
I-17	3-Isoxazolyl	3-Isoxazolyl	-CH ₂ -	0	0	NH ₂
I-18	4-Oxazolyl	4-Oxazolyl	-CH ₂ -	0	0	NH ₂

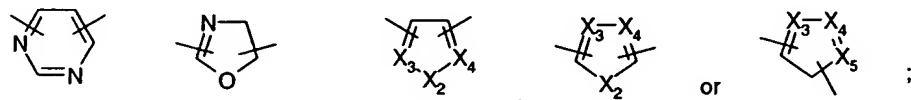
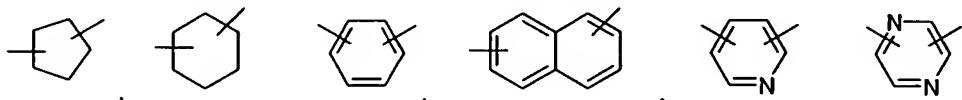
No.	Ar ₁	Ar ₂	Y	m	n	NR ₃ R ₄
I-19	2-Oxazolyl	2-Oxazolyl	-CH ₂ -	0	0	NH ₂
I-20	4- Imidazolyl	4- Imidazolyl	-CH ₂ -	0	0	NH ₂
I-21	2- Imidazolyl	2- Imidazolyl	-CH ₂ -	0	0	NH ₂
I-22	Phenyl	3-Thienyl	-CH ₂ -	0	0	NH ₂
I-23	2-Pyridyl	2-Pyridyl	-CH ₂ -	0	0	NH ₂
I-24	3-Pyridyl	3-Pyridyl	-CH ₂ -	0	0	NH ₂
I-25	4-Pyridyl	4-Pyridyl	-CH ₂ -	0	0	NH ₂
I-26	3-Thienyl	3-Thienyl	-CH ₂ -	0	0	NH(CH ₂) ₂ OH
I-27	3-Thienyl	3-Thienyl	-CH ₂ -	0	0	NH(CH ₂) ₂ -N- piperidyl
I-28	3-Thienyl	3-Thienyl	-CH ₂ -	0	0	NH(CH ₂) ₂ -N- morpholinoyl
I-29	3-Thienyl	3-Thienyl	-CH ₂ -	0	0	NH(CH ₃)
I-30	3-Thienyl	3-Thienyl	-CH ₂ -	0	0	NH(CH ₂ -[2- pyridyl])
I-31	3-Thienyl	3-Thienyl	-CH ₂ -	0	0	NH(CH ₂ -[3- pyridyl])
I-32	3-Thienyl	3-Thienyl	-CH ₂ -	0	0	NH(CH ₂ -[4- pyridyl])
I-33	3-Thienyl	3-Thienyl	-CH ₂ -	0	0	
I-34	3-Thienyl	3-Thienyl	-CH ₂ -	0	0	
I-35	3-Thienyl	3-Thienyl		1	0	NH ₂
I-36	Phenyl	3-Thienyl	-CH ₂ -	1	0	NH ₂

No.	Ar ₁	Ar ₂	Y	m	n	NR ₃ R ₄
I-37	2-Thiazolyl	Phenyl	-CH ₂ -	0	0	NH ₂
I-38	2-Thiazolyl	2-Thienyl	-CH ₂ -	0	0	NH ₂

In certain preferred embodiments of the present invention, there are provided compounds of formula (II) or (II-A) where q=1.

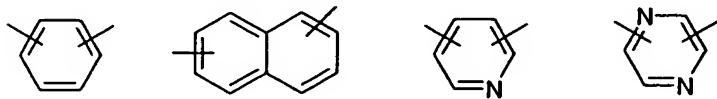
In another embodiment of formula (II-A), X is a bond, -CH₂CH₂-, -O-, -N(CH₃)-, or -CH=CH-, and preferably X is a bond.

5 In certain embodiments of formula (II-A), Y is -O-, -S(O)_y-, -N(R₈)-, C₁-C₄ alkylene, -CR_{8A}=CR_{8B}-, -CH=CH-CH(R₈)-, -CH(R₈)-CH=CH-, -C≡C-,

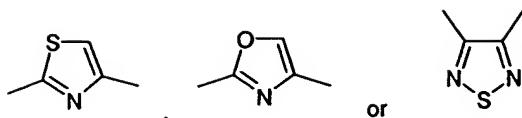


wherein X₂ is -CH₂-, -O-, -S(O)_y-, or -N(R₈)-; and X₃, X₄, and X₅ are each independently selected from -CH-, or -N-. In other preferred embodiments, Y is -O-, -S(O)_y-, or -

10 N(R₈)-. In another preferred embodiment, Y is C₁-C₄ alkylene. In an additional embodiment, Y is -CR_{8A}=CR_{8B}-, -CH=CH-CH(R₈)-, -CH(R₈)-CH=CH-, or -C≡C-. In certain preferred embodiments, Y is C₆-C₁₀ arylene or heteroarylene, and preferably, m=0 or 1 and n=0 or 1. More preferably, Y is



15 wherein X₂ is -CH₂-, -O-, -S(O)_y-, or -N(R₈)-; and X₃, X₄, and X₅ are each independently selected from -CH-, or -N-. Most preferably, Y is phenylene. In another more preferred embodiment, Y is

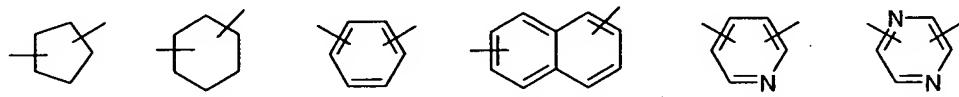


In further preferred embodiments, Y is C₃-C₈ cycloalkylene or heterocyclylene.

Preferably, Y is



5 In additional embodiments of formula (II-A), rings A and B, together with the carbon atoms to which they are attached, are each independently selected from phenylene, thienylene, isothiazolylene, pyridylene, oxazolylene, isoxazolylene, thiazolylene, imidazolylene. In a preferred embodiment, ring A is phenylene, and more preferably, rings A and B are phenylene. In another preferred embodiment, rings A and 10 B are thienylene, and more preferably, rings A and B are 2,3-thienylene. In preferred embodiments, q=1. In further preferred embodiments, ring A is phenylene and ring B is 2,3-thienylene. In other preferred embodiments, X is a bond, -CH₂CH₂-, -O-, -N(CH₃)-, or -CH=CH-. In a more preferred embodiment, Y is -O-, -S(O)_y-, -N(R₈)-, C₁-C₄ alkylene, -CR_{8A}=CR_{8B}-, -CH=CH-CH(R₈)-, -CH(R₈)-CH=CH-, -C≡C-,

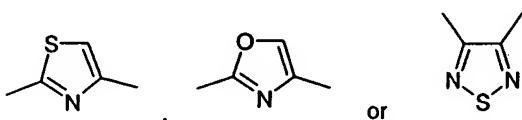


15 wherein X₂ is -CH₂-, -O-, -S(O)_y-, or -N(R₈)-, and X₃, X₄, and X₅ are each independently selected from -CH-, or -N-. In other preferred embodiments, Y is -O-, -S(O)_y-, or -N(R₈)-. In another preferred embodiment, Y is C₁-C₄ alkylene. In an additional embodiment, Y is -CR_{8A}=CR_{8B}-, -CH=CH-CH(R₈)-, -CH(R₈)-CH=CH-, or -C≡C-. In certain 20 preferred embodiments, Y is C₆-C₁₀ arylene or heteroarylene, and preferably, m=0 or 1 and n=0 or 1. More preferably, Y is



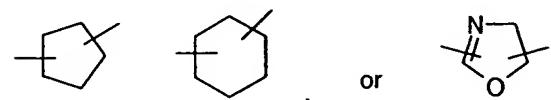
wherein X_2 is $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}(\text{O})_y-$, or $-\text{N}(\text{R}_8)-$; and X_3 , X_4 , and X_5 are each independently selected from $-\text{CH}-$, or $-\text{N}-$. Most preferably, Y is phenylene. In another more preferred embodiment, Y is

5



In further preferred embodiments, Y is $\text{C}_3\text{-C}_8$ cycloalkylene or heterocyclylene.

Preferably, Y is



In an especially preferred embodiment, X is a bond, and Y is $-\text{CH}_2-$ and $n=0$.

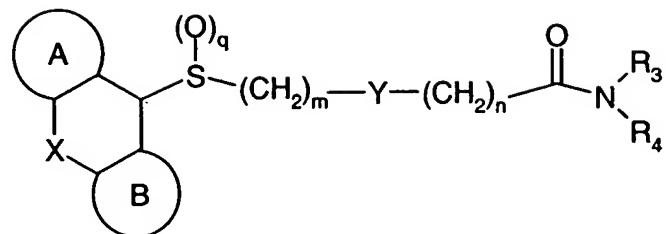
10 Preferred embodiments of formula (II) are compounds wherein ring A is selected from thiophene, isothiazole, phenyl, oxazole, isoxazole, thiazole, and imidazole. Other preferred embodiments are those where the benzo ring and ring A are each independently substituted.

Other preferred embodiments of formula (II) are given below:

15 1) Compounds in which A is benzo and X is a bond, i.e. $-(\text{CH}_2)_m-$, where $m=0$;
 2) Compounds in which A is benzo and X is $-\text{O}-$;
 3) Compounds in which A is benzo and X is $-\text{NCH}_3$;
 4) Compounds in which A is benzo and X is $-\text{S}-$; and
 5) Compounds in which R_3 and R_4 are taken together with the nitrogen to which
 20 they are attached to form a morpholine ring.

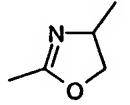
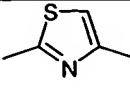
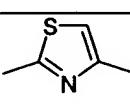
In a particularly preferred embodiment of formula (II-A), there are provided compounds as represented in Table 2:

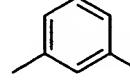
Table 2

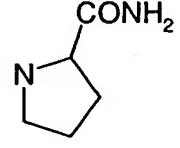
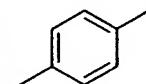


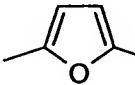
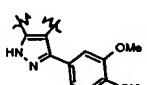
(II-A)

No.	A	B	X	Y	m	n	NR ₃ R ₄
II-1	Benzo	Benzo	bond	-CH ₂ -	1	0	NH ₂
II-2	Benzo	Benzo	bond	-CH ₂ -	1	0	NMe ₂
II-3	Benzo	Benzo	bond	-CH ₂ -	1	1	NH ₂
II-4	Benzo	Benzo	bond	-CH ₂ -	1	0	NHCH(CH ₃) -CONH ₂
II-5	Benzo	Benzo	bond	-CH ₂ -	1	0	morpholino
II-6	Benzo	Benzo	bond	-CH ₂ -	2	1	NH ₂
II-7	Benzo	Benzo	bond	-CH ₂ -	2	1	NMe ₂
II-8	Benzo	Benzo	bond	-CH(CH ₃)-	1	0	NH ₂
II-9	Benzo	Benzo	bond	-CH ₂ -	0	0	NHCH(CH ₃) -CONH ₂
II-10	Benzo	Benzo	bond		1	0	NH ₂
II-11	Benzo	Benzo	bond	-C(CH ₃) ₂ -	1	0	NH ₂
II-12	Benzo	Benzo	bond		1	0	NH ₂
II-13	Benzo	Benzo	-CH ₂ CH ₂ -	-CH ₂ -	1	0	NH ₂
II-14	Benzo	Benzo	-CH ₂ CH ₂ -	-CH(CH ₃)-	1	0	NH ₂

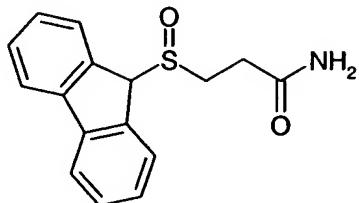
No.	A	B	X	Y	m	n	NR ₃ R ₄
II-15	Benzo	Benzo	bond		1	0	NH ₂
II-16	Benzo	Benzo	bond		1	0	NH ₂
II-17	Benzo	Benzo	bond		1	0	NMe ₂
II-18	Benzo	Benzo	-CH=CH-	-CH ₂ -	2	1	NH ₂
II-19	Benzo	Benzo	-CH=CH-	-C(CH ₃) ₂ -	1	0	NH ₂
II-20	Benzo	Benzo	-O-	-CH ₂ -	2	1	NH ₂
II-21	Benzo	Benzo	-O-	-CH(CH ₃)-	1	0	NH ₂
II-22	2,3- Thieno	2,3-Thieno	bond	-CH ₂ -	0	0	NH ₂
II-23	Benzo	Benzo	bond	-CH ₂ -	0	0	NH ₂
II-24	Benzo	Benzo	bond	-CH ₂ -	0	0	NHCH(CH ₃) -CONMe ₂
II-25	Benzo	Benzo	-CH ₂ CH ₂ -	-CH ₂ -	0	0	NH ₂
II-26	Benzo	Benzo	-CH ₂ CH ₂ -	-CH ₂ -	0	0	N(CH ₃) ₂
II-27	Benzo	Benzo	-O-	-CH ₂ -	0	0	NH ₂
II-28	Benzo	Benzo	-N(CH ₃)-	-CH ₂ -	0	0	NH ₂
II-29	Benzo	Benzo	-S-	-CH ₂ -	0	0	NH ₂
II-30	Benzo	Benzo	bond	-CH ₂ -	0	0	NH(CH ₃)
II-31	Benzo	Benzo	bond	-CH ₂ -	0	0	NH(CH ₂ CH ₂ -NH[t-Boc])
II-32	Benzo	Benzo	bond	-CH ₂ -	0	0	NH(CH ₂ -[2- pyridyl])
II-33	Benzo	Benzo	bond	-CH ₂ -	0	0	NH(CH ₂ -[3- pyridyl])
II-34	Benzo	Benzo	bond	-CH ₂ -	0	0	NH(CH ₂ CH ₂ OH)

No.	A	B	X	Y	m	n	NR ₃ R ₄
II-35	Benzo	Benzo	bond	-CH ₂ -	0	0	N(CH ₃) ₂
II-36	Benzo	Benzo	bond	-CH ₂ -	0	0	
II-37	Benzo	Benzo	-CH=CH-	-CH ₂ -	0	0	NH ₂
II-38	Benzo	Benzo	bond		1	0	N(CH ₃) ₂
II-39	Benzo	Benzo	bond	-CH ₂ -	0	0	NHOH
II-40	Benzo	Benzo	bond	-CH ₂ -	0	0	NHCH ₂ CON H ₂
II-41	Benzo	Benzo	bond	-CH ₂ -	0	0	NH(CH ₂) ₂ - CONH ₂
II-42	Benzo	Benzo	bond	-CH ₂ -	0	0	NH(CH ₂) ₂ F
II-43	Benzo	Benzo	bond	-CH ₂ -	0	0	NET ₂
II-44	Benzo	Benzo	bond	-CH ₂ -	0	0	NH-(<i>r</i>)- CH(CH ₃)CO NH ₂
II-45	Benzo	Benzo	bond	-CH ₂ -	0	0	NH-(<i>r</i>)- CH(CH ₃)- C ₆ H ₅
II-46	Benzo	Benzo	bond	-CH ₂ -	0	0	NH-(<i>s</i>)- CH(CH ₃)- CH ₂ OH
II-47	Benzo	Benzo	bond	-CH ₂ -	0	0	NH-(<i>s</i>)- CH(CH ₃)- CO ₂ Me
II-48	Benzo	Benzo	bond	-CH ₂ -	0	0	NH-(<i>s</i>)- CH(CH ₃)CO NH ₂

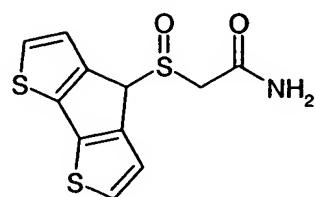
No.	A	B	X	Y	m	n	NR ₃ R ₄
II-49	Benzo	Benzo	bond	-CH ₂ -	0	0	NH-(s)-CH(CH ₃)CO NH ₂
II-50	Benzo	Benzo	bond	-CH ₂ -	0	0	NH-(s)-CH(CH ₃)CO NMe ₂
II-51	Benzo	Benzo	bond	-CH ₂ -	0	0	NH-(s)-CH(CH ₂ OH)CONH ₂
II-52	Benzo	Benzo	bond	-CH ₂ -	0	0	NH-(s)-CH[CH(OH)CH ₃]CONH ₂
II-53	Benzo	Benzo	bond	-CH ₂ -	0	0	
II-54	Benzo	Benzo	bond	-CH(CH ₃)-	0	0	NH ₂
II-55	Benzo	Benzo	-O-	-CH ₂ -	1	0	NH ₂
II-56	Benzo	Benzo	-O-	-CH ₂ -	0	0	N(CH ₃) ₂
II-57	Benzo	Benzo	-O-	-CH ₂ -	0	0	NH-(s)-CH(CH ₃)CO NH ₂
II-58	Benzo	Benzo	-CH ₂ CH ₂ -	-CH ₂ CH ₂ -	0	0	NH ₂
II-59	Benzo	Benzo	-CH ₂ CH ₂ -	-CH(CH ₃)-	1	0	NH ₂
II-60	Benzo	Benzo	bond		0	0	NH ₂
II-61	Benzo	Benzo	-CH=CH-	-C(CH ₃) ₂ -	1	0	NH ₂
II-62	Benzo	Benzo	-CH ₂ CH ₂ -	-CH ₂ -	1	0	NH-

No.	A	B	X	Y	m	n	NR ₃ R ₄
							CH(CH ₃)CO NH ₂
II-63	Benzo	Benzo	-CH ₂ CH ₂ -	-CH ₂ -	1	0	morpholino
II-64	Benzo	Benzo	bond		1	0	NH ₂
II-65	Benzo	Benzo	bond	-CH=CH-	0	0	NH ₂
II-66		Benzo	bond	-CH ₂ -	0	0	NH ₂

For example, compounds II-1 and II-22 have the following structures:



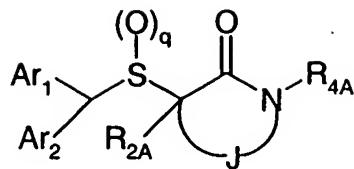
II-1



II-22

In additional embodiments of the present invention, there are provided

5 compounds of formula (V):



wherein:

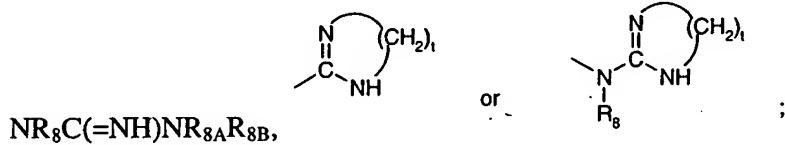
Ar₁ and Ar₂ are each independently selected from C₆-C₁₀ aryl or heteroaryl;

5 wherein each of Ar₁ or Ar₂ may be independently optionally substituted with 1-3 substituents independently selected from:

a) H, C₆-C₁₀ aryl, heteroaryl, F, Cl, Br, I, -CN, -CF₃, -NO₂, -OH, -OR₇, -O(CH₂)_pNR₉R₁₀, -OC(=O)R₇, -OC(=O)NR₉R₁₀, -O(CH₂)_pOR₈, -CH₂OR₈, -NR₉R₁₀, -NR₈S(=O)₂R₇, -NR₈C(=O)R₇, or -NR₈C(=S)R₇;

10 b) -CH₂OR₁₁;

c) -NR₈C(=O)NR₉R₁₀, -NR₈C(=S)NR₉R₁₀, -CO₂R₁₂, -C(=O)R₁₃, -C(=O)NR₉R₁₀, -C(=S)NR₉R₁₀, -CH=NOR₁₂, -CH=NR₇, -(CH₂)_pNR₉R₁₀, -(CH₂)_pNHR₁₁, -CH=NNR₁₂R_{12A}, -C(=NR₈)NR_{8A}R_{8B} -NR₈C(=NH)R_{8A}, -



15 d) -S(O)_yR₇, -(CH₂)_pS(O)_yR₇, -CH₂S(O)_yR₇; and

e) C₁-C₈ alkyl, C₂-C₈ alkenyl, or C₂-C₈ alkynyl, where:

3) each alkyl, alkenyl, or alkynyl group is unsubstituted; or

4) each alkyl, alkenyl or alkynyl group is independently substituted with 1 to 3 groups independently selected from C₆-C₁₀ aryl, heteroaryl, F, Cl, Br, I, CF₃, -CN, -NO₂, -OH, -OR₇, -CH₂OR₈, -NR₉R₁₀, -O-(CH₂)_p-OH, -S-(CH₂)_p-OH, -X₁(CH₂)_pOR₇, X₁(CH₂)_pNR₉R₁₀, -X₁(CH₂)_pC(=O)NR₉R₁₀, -X₁(CH₂)_pC(=S)NR₉R₁₀, -X₁(CH₂)_pOC(=O)NR₉R₁₀, -X₁(CH₂)_pCO₂R₈, -X₁(CH₂)_pS(O)_yR₇, -X₁(CH₂)_pNR₈C(=O)NR₉R₁₀, -C(=O)R₁₃, -CO₂R₁₂, -OC(=O)R₇, -C(=O)NR₉R₁₀, -

20 25

OC(=O)NR₁₂R_{12A}, O-tetrahydropyranyl, -C(=S)NR₉R₁₀, -
CH=NNR₁₂R_{12A}, -CH=NOR₁₂, -CH=NR₇, -
CH=NNHCH(N=NH)NH₂, -NR₈CO₂R₇, -NR₈C(=O)NR₉R₁₀, -
NR₈C(=S)NR₉R₁₀, -NHC(=NH)NH₂, -NR₈C(=O)R₇, -
NR₈C(=S)R₇, -NR₈S(=O)₂R₇, -S(O)_yR₇, -S(=O)₂NR₁₂R_{12A}, -
P(=O)(OR₈)₂, -OR₁₁, and a C₅-C₇ monosaccharide where each
hydroxyl group of the monosaccharide is independently either
unsubstituted or is replaced by H, C₁-C₄ alkyl, C₁-C₄ alkoxy, or -
O-C(=O)R₇;

5

10 X₁ is -O-, -S-, -N(R₈)-;
J is C₂-C₄ alkylene or Q-CO-;
Q is C₁-C₃ alkylene;
R_{2A} is H, C₁-C₆ alkyl, aryl or heteroaryl;
R_{4A} is H, C₁-C₆ alkyl, aryl or heteroaryl;

15 R₇ is C₁-C₆ alkyl, C₆-C₁₀ aryl, or heteroaryl;
R₈, R_{8A} and R_{8B} are each independently H, C₁-C₄ alkyl, or C₆-C₁₀ aryl;
R₉ and R₁₀ are independently selected from H, C₁-C₄ alkyl, and C₆-C₁₀ aryl; or R₉ and
R₁₀ together with the nitrogen to which they are attached, form a 3-7 member
heterocyclic ring;

20 R₁₁ is the residue of an amino acid after the hydroxyl group of the carboxyl group is
removed;
R₁₂ and R_{12A} are each independently selected from H, C₁-C₆ alkyl, cycloalkyl, C₆-C₁₀
aryl, and heteroaryl; or R₁₂ and R_{12A}, together with the nitrogen to which they are
attached, form a 5-7 member heterocyclic ring;

25 R₁₃ is H, C₁-C₆ alkyl, cycloalkyl, C₆-C₁₀ aryl, heteroaryl, -C(=O)R₇, -C(=O)NR₉R₁₀, or -
C(=S)NR₉R₁₀;

p is from 1, 2, 3, or 4;

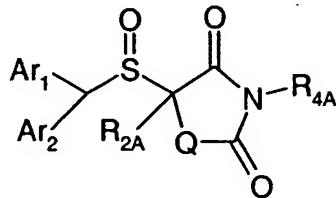
q is 0, 1, or 2;

t is 2, 3, or 4;

30 y is 0, 1 or 2;
and the stereoisomeric forms, mixtures of stereoisomeric forms, or pharmaceutically
acceptable salt and ester forms thereof.

In particular embodiments of formula (V), Ar_1 and Ar_2 are each independently phenyl or thienyl, preferably both are phenyl; q is preferably 1; when J is C_2 - C_4 alkylene, it is preferably C_2 alkylene or C_3 alkylene; R_{2A} is preferably H, C_1 - C_6 alkyl and R_{4A} is preferably phenyl, thienyl or pyridyl, and more preferably, R_{4A} is phenyl.

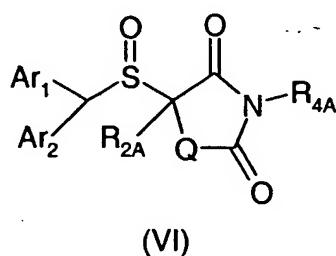
5 In another particular embodiment of formula (V), there are provided compounds where q is 1; and J is Q-CO to form a compound of formula (VI):



(VI)

wherein Q is C_1 - C_3 alkylene. In certain embodiments, Ar_1 and Ar_2 are each independently phenyl or thienyl, preferably both are phenyl; and Q is C_1 alkylene or C_2 alkylene. Certain preferred embodiments of formula (VI) are provided in Table 2A:

10

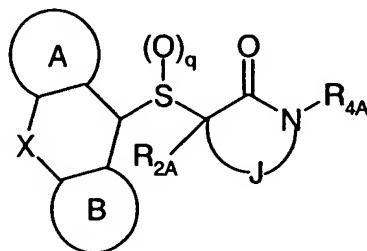
Table 2A

(VI)

No.	Ar_1	Ar_2	R_{2A}	Q	R_{4A}
VI-1	Phenyl	Phenyl	H	CH_2	H
VI-2	Phenyl	Phenyl	H	CH_2	CH_3
VI-3	Phenyl	Phenyl	H	CH_2	$(CH_2)_2OMe$
VI-4	Phenyl	Phenyl	H	CH_2	$(CH_2)_2OH$
VI-5	Phenyl	Phenyl	H	CH_2	$(S)-CH(CH_3)CH_2OH$
VI-6	4-Fluorophenyl	4-Fluorophenyl	H	CH_2	CH_3

No.	Ar ₁	Ar ₂	R _{2A}	Q	R _{4A}
VI-7	3-Thienyl	3-Thienyl	H	CH ₂	H
VI-8	3-Thienyl	Phenyl	H	CH ₂	H
VI-9	Phenyl	Phenyl	H	(CH ₂) ₂	H

In additional embodiments of the present invention, there are provided compounds of formula (VII):



(VII)

5

wherein

X is a bond, -CH₂CH₂-, -O-, -S(O)_y-, -N(R₈)-, -CHN(R₈)-, -CH=CH-, -CH₂-CH=CH-, C(=O), -C(R₈)=N-, -N=C(R₈)-, -C(=O)-N(R₈)-, or -NR₈-C(=O)-;

10 Rings A and B, together with the carbon atoms to which they are attached, are each independently selected from:

- a) a 6-membered aromatic carbocyclic ring in which from 1 to 3 carbon atoms may be replaced by hetero atoms selected from oxygen, nitrogen and sulfur; and
- b) a 5-membered aromatic carbocyclic ring in which either:
 - i) one carbon atom is replaced with an oxygen, nitrogen, or sulfur atom;
 - ii) two carbon atoms are replaced with a sulfur and a nitrogen atom, an oxygen and a nitrogen atom, or two nitrogen atoms; or
 - iii) three carbon atoms are replaced with three nitrogen atoms, one oxygen and two nitrogen atoms, or one sulfur and two nitrogen atoms;

15 20 wherein Ring A and Ring B may each independently be substituted with 1-3 substituents selected from:

a) H, C₆-C₁₀ aryl, heteroaryl, F, Cl, Br, I, -CN, -CF₃, -NO₂, -OH, -OR₇, -O(CH₂)_pNR₉R₁₀, -OC(=O)R₇, -OC(=O)NR₉R₁₀, -O(CH₂)_pOR₈, -CH₂OR₈, -NR₉R₁₀, -NR₈S(=O)₂R₇, -NR₈C(=O)R₇, or -NR₈C(=S)R₇;

b) -CH₂OR₁₁;

5 c) -NR₈C(=O)NR₉R₁₀, -NR₈C(=S)NR₉R₁₀, -CO₂R₁₂, -C(=O)R₁₃, -C(=O)NR₉R₁₀, -C(=S)NR₉R₁₀, -CH=NOR₁₂, -CH=NR₇, -(CH₂)_pNR₉R₁₀, -(CH₂)_pNHR₁₁, -CH=NNR₁₂R_{12A}, -C(=NR₈)NR_{8A}R_{8B} -NR₈C(=NH)R_{8A}, -NR₈C(=NH)NR_{8A}R_{8B},

d) -S(O)_yR₇, -(CH₂)_pS(O)_yR₇, -CH₂S(O)_yR₇; and

10 e) C₁-C₈ alkyl, C₂-C₈ alkenyl, or C₂-C₈ alkynyl, where:

1) each alkyl, alkenyl, or alkynyl group is unsubstituted; or

2) each alkyl, alkenyl or alkynyl group is independently substituted with 1 to 3 groups independently selected from C₆-C₁₀ aryl, heteroaryl, F, Cl, Br, I, CF₃, -CN, -NO₂, -OH, -OR₇, -CH₂OR₈, -NR₉R₁₀, -O-(CH₂)_p-OH, -S-(CH₂)_p-OH, -X₁(CH₂)_pOR₇, X₁(CH₂)_pNR₉R₁₀, -X₁(CH₂)_pC(=O)NR₉R₁₀, -X₁(CH₂)_pC(=S)NR₉R₁₀, -X₁(CH₂)_pOC(=O)NR₉R₁₀, -X₁(CH₂)_pCO₂R₈, -X₁(CH₂)_pS(O)_yR₇, -X₁(CH₂)_pNR₈C(=O)NR₉R₁₀, -C(=O)R₁₃, -CO₂R₁₂, -OC(=O)R₇, -C(=O)NR₉R₁₀, -OC(=O)NR₁₂R_{12A}, O-tetrahydropyranyl, -C(=S)NR₉R₁₀, -CH=NNR₁₂R_{12A}, -CH=NOR₁₂, -CH=NR₇, -CH=NNHCH(N=NH)NH₂, -NR₈CO₂R₇, -NR₈C(=O)NR₉R₁₀, -NR₈C(=S)NR₉R₁₀, -NHC(=NH)NH₂, -NR₈C(=O)R₇, -NR₈C(=S)R₇, -NR₈S(=O)₂R₇, -S(O)_yR₇, -S(=O)₂NR₁₂R_{12A}, -P(=O)(OR₈)₂, -OR₁₁, and a C₅-C₇ monosaccharide where each hydroxyl group of the monosaccharide is independently either unsubstituted or is replaced by H, C₁-C₄ alkyl, C₁-C₄ alkoxy, or -O-C(=O)R₇;

20 J is C₂-C₄ alkylene or Q-CO-;

25 Q is C₁-C₃ alkylene;

R_{2A} is H, C₁-C₆ alkyl, aryl or heteroaryl;

R_{4A} is H, C₁-C₆ alkyl, aryl or heteroaryl;

R₇ is C₁-C₆ alkyl, C₆-C₁₀ aryl, or heteroaryl;

R₈, R_{8A} and R_{8B} are each independently H, C₁-C₄ alkyl, or C₆-C₁₀ aryl;

5 R₉ and R₁₀ are independently selected from H, C₁-C₄ alkyl, and C₆-C₁₀ aryl; or R₉ and R₁₀ together with the nitrogen to which they are attached, form a 3-7 member heterocyclic ring;

R₁₁ is the residue of an amino acid after the hydroxyl group of the carboxyl group is removed;

10 R₁₂ and R_{12A} are each independently selected from H, C₁-C₆ alkyl, cycloalkyl, C₆-C₁₀ aryl, and heteroaryl; or R₁₂ and R_{12A}, together with the nitrogen to which they are attached, form a 5-7 member heterocyclic ring;

R₁₃ is H, C₁-C₆ alkyl, cycloalkyl, C₆-C₁₀ aryl, heteroaryl, -C(=O)R₇, -C(=O)NR₉R₁₀, or -C(=S)NR₉R₁₀;

15 X₁ is -O-, -S-, -N(R₈)-;

p is from 1 to 4;

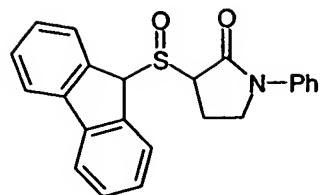
q is 0, 1, or 2;

t is 2, 3, or 4;

y is 0, 1 or 2;

20 and the stereoisomeric forms, mixtures of stereoisomeric forms, or pharmaceutically acceptable salt and ester forms thereof.

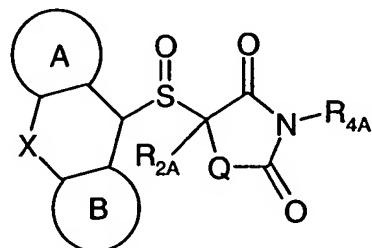
In particular embodiments of formula (VII), rings A and B are each independently benzo or thieno, preferably both are benzo; q is preferably 1; when J is C₂-C₄ alkylene, it is preferably C₂ alkylene or C₃ alkylene; R_{2A} is preferably H, C₁-C₆ alkyl and R_{4A} is preferably phenyl, thienyl or pyridyl, and more preferably, R_{4A} is phenyl. A preferred embodiment is a compound of formula (VII-1):



(VII-1)

In another particular embodiment of formula (VII), there are provided compounds where q is 1; and J is $Q\text{-CO-}$ to form a compound of formula (VIII):

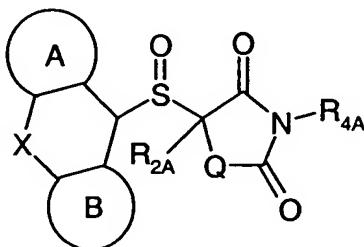
5



(VIII)

wherein Q is $C_1\text{-}C_3$ alkylene. In certain embodiments, rings A and B are both preferably benzo; X is preferably a bond or $-\text{O}-$; and Q is C_1 alkylene or C_2 alkylene. Certain 10 preferred embodiments of formula (VIII) are provided in Table 2B:

Table 2B



15

(VIII)

N.	A	B	X	R _{2A}	Q	R _{4A}
VIII-1	Benzo	Benzo	bond	H	CH ₂	H

No.	A	B	X	R _{2A}	Q	R _{4A}
VIII-2	Benzo	Benzo	bond	H	CH ₂	Me
VIII-3	Benzo	Benzo	bond	H	CH ₂	(CH ₂) ₂ OMe
VIII-4	Benzo	Benzo	bond	H	CH ₂	(CH ₂) ₂ OH
VIII-5	Benzo	Benzo	bond	H	CH ₂	CH(CH ₃)CH ₂ OH
VIII-6	Benzo	Benzo	bond	H	CH ₂	OH
VIII-7	Benzo	Benzo	bond	H	CH ₂	CH ₂ -(4-methoxyphenyl)
VIII-8	Benzo	Benzo	bond	H	CH ₂	Ph
VIII-9	Benzo	Benzo	bond	H	(CH ₂) ₂	H

Definitions

As used herein, the term "alkyl" refers to a substituted or unsubstituted, branched or straight hydrocarbon chain of 1 to 8 carbon atoms, which is formed by the removal of one hydrogen atom. In certain preferred embodiments, the alkyl group contains from 1 to 6 carbon atoms. In other preferred embodiments, the alkyl group contains from 1 to 4 carbon atoms. A designation such as "C₁-C₄ alkyl" refers to an alkyl radical containing from 1 to 4 carbon atoms. Examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl, 2-methylpentyl, hexyl, 2-methylhexyl, 2,3-dimethylhexyl, heptyl, octyl, etc.

As used herein, the term "lower alkyl," refers to a C₁ to C₆ saturated straight chain, branched, or cyclic hydrocarbon, which are optionally substituted. Lower alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, cyclopentyl, isopentyl, neopentyl, n-hexyl, isohexyl, cyclohexyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and the like.

As used herein, "alkenyl" refers to a substituted or unsubstituted, straight or branched hydrocarbon chain containing from 2 to 8 carbon atoms having one or more carbon-carbon double bonds which may occur in any stable point along the chain, and which is formed by removal of one hydrogen atom. A designation "C₂-C₈ alkenyl" refers to an alkenyl radical containing from 2 to 8 carbon atoms. Examples include ethenyl, propenyl, isopropenyl, 2,4-pentadienyl, etc.

As used herein, "alkynyl" refers to a substituted or unsubstituted, straight or branched hydrocarbon radical containing from 2 to 8 carbon atoms, having one or more

carbon-carbon triple bonds which may occur in any stable point along the chain, and which is formed by removal of one hydrogen atom. A designation "C₂-C₈ alkynyl" refers to an alkynyl radical containing from 2 to 8 carbon atoms. Examples include ethynyl, propynyl, isopropynyl, 3,5-hexadiynyl, etc.

5 As used herein, "carbocycle" or "carbocyclic" refer to a substituted or unsubstituted, stable monocyclic or bicyclic hydrocarbon ring which is saturated, partially unsaturated or unsaturated, and contains from 3 to 10 carbon atoms. Accordingly the carbocyclic group may be aromatic or non-aromatic. The bonds connecting the endocyclic carbon atoms of a carbocyclic group may be single, double, 10 triple, or part of a fused aromatic moiety. Carbocycles are intended to include the "cycloalkyl" and "aryl" compounds defined herein.

As used herein, the term "cycloalkyl" refers to a substituted or unsubstituted hydrocarbon ring of 3 to 7 carbon atoms formed by the removal of one hydrogen atom. A designation such as "C₅-C₇ cycloalkyl" refers to a cycloalkyl radical containing from 5 15 to 7 carbon atoms. Examples include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.

As used herein, the terms "heterocycle" or "heterocyclic" refer to a substituted or unsubstituted, saturated, partially unsaturated or unsaturated, stable 3 to 10 membered monocyclic or bicyclic ring wherein at least one member of the ring is a hetero atom. 20 Accordingly the heterocyclic group may be aromatic or non-aromatic. Typically, heteroatoms include, but are not limited to, oxygen, nitrogen, sulfur, selenium, and phosphorus atoms. Preferable heteroatoms are oxygen, nitrogen and sulfur. The nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen may be optionally substituted in non-aromatic rings. The bonds connecting the endocyclic atoms 25 of a heterocyclic group may be single, double, triple, or part of a fused aromatic moiety. Heterocycles are intended to include "heterocyclyl" and "heteroaryl" compounds defined herein.

As used herein, "heterocyclyl" refers to a substituted or unsubstituted, saturated, or partially unsaturated, stable 3 to 7 membered heterocyclic ring which is formed by 30 removal of one hydrogen atom. Examples include epoxyethyl, pyrrolidyl, pyrazolidinyl, piperidyl, pyranyl, oxazolinyl, morpholino, morpholinyl, piperazinyl, etc.

Examples of heterocycles include, but are not limited to, 2-pyrrolidinyl, 2H-pyrrolyl, 4-piperidinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, isoxazolyl, morpholinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 5 oxazolidinyl, oxazolyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, tetrahydrofuran, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and tetrazole. Suitable heterocycles are also disclosed in *The Handbook of Chemistry and Physics*, 76th Edition, CRC Press, Inc., 1995-1996, pages 2-25 to 2-26, the disclosure of which is hereby incorporated by reference.

Preferred heterocyclic groups formed with a nitrogen atom include, but are not limited to, pyrrolidinyl, piperidinyl, piperidino, morpholinyl, morpholino, thiomorpholino, N-methylpiperazinyl, indolyl, isoindolyl, imidazole, imidazoline, oxazoline, oxazole, triazole, thiazoline, thiazole, isothiazole, thiadiazoles, triazines, isoxazole, oxindole, indoxyl, pyrazole, pyrazolone, pyrimidine, pyrazine, quinoline, isoquinoline, and tetrazole groups.

Preferred heterocyclic groups formed with an oxygen atom include, but are not limited to, furan, tetrahydrofuran, pyran, benzofurans, isobenzofurans, and tetrahydropyran groups. Preferred heterocyclic groups formed with a sulfur atom include, but are not limited to, thiophene, thianaphthene, tetrahydrothiophene, tetrahydrothiopyran, and benzothiophenes.

Preferred aromatic heterocyclic groups include, but are not limited to, pyridyl, pyrimidyl, pyrrolyl, furyl, thienyl, imidazolyl, triazolyl, tetrazolyl, quinolyl, isoquinolyl, benzoimidazolyl, thiazolyl, pyrazolyl, and benzothiazolyl groups.

As used herein, the term "substituted" refers to replacement of one or more hydrogen atoms on an indicated group with a selected group referred to herein as a "substituent", provided that the substituted atom's valency is not exceeded, and that the substitution results in a stable compound. A substituted group has 1 to 5, preferably 1 to 3, and more preferably 1, independently selected substituents. Preferred substituents

include, but are not limited to F, Cl, Br, I, OH, OR, NH₂, NR₂, NHOH, NO₂, CN, CF₃, CF₂CF₃, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₇ cycloalkyl, heterocyclyl, C₆-C₁₀ aryl, heteroaryl, arylalkyl, C(=O)R, COOH, CO₂R, O-C(=O)R, C(=O)NRR', NRC(=O)R', NR₂CO₂R', OC(=O)NRR', -NRC(=O)NRR', -NRC(=S)NRR', and -SO₂NRR', wherein R and R' are each independently hydrogen, C₁-C₆ alkyl, or C₆-C₁₀ aryl.

As used herein, the term "aryl" refers to a substituted or unsubstituted, aromatic carbocyclic ring containing from 6 to 10 carbon atoms, which is formed by removal of one hydrogen atom. Examples include phenyl, naphthyl, indenyl, etc.

10 As used herein, the term "heteroaryl" refers to a substituted or unsubstituted 5 to 10 membered aromatic heterocyclic ring, which is formed by removal of one hydrogen atom. Examples include pyrrolyl, pyridyl, pyrimidinyl, pyrazinyl, tetrazolyl, indolyl, quinolinyl, purinyl, imidazolyl, thienyl, thiazolyl, benzothiazolyl, furanyl, benzofuranyl, 1,2,4-thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, isoquinolyl, benzothienyl, 15 isobenzofuranyl, pyrazolyl, carbazolyl, benzimidazolyl, isoxazolyl, etc.

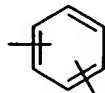
As used herein, the term "alkylene" refers to a substituted or unsubstituted, branched or straight chained hydrocarbon of 1 to 8 carbon atoms, which is formed by the removal of two hydrogen atoms. A designation such as "C₁-C₄ alkylene" refers to an alkylene radical containing from 1 to 4 carbon atoms. Examples include methylene (-CH₂-), propylidene (CH₃CH₂CH=), 1,2-ethandiyil (-CH₂CH₂-), etc.

20 As used herein, the term "cycloalkylene" refers to substituted or unsubstituted carbocyclic ring of 3 to 8 carbon atoms, which is formed by removal of two hydrogen atoms. A designation such as "C₃-C₈ cycloalkylene" refers to an cycloalkylene radical containing from 3 to 8 carbon atoms. Examples include cyclopropylene (-C₃H₄-), 25 cyclopentylene (-C₅H₈-), cyclohexylene (-C₆H₁₀-), etc.

As used herein, the term "heterocyclylene" refers to a substituted or unsubstituted, saturated, or partially unsaturated, stable 3 to 7 membered heterocyclic ring, which is formed by removal of two hydrogen atoms. Examples include epoxyethylene, pyrrolidylene, pyrrolidylidene, pyrazolidinylene, piperidylene, 30 pyranylene, morpholinylidene, etc.

As used herein, the term "arylene" refers to a substituted or unsubstituted aromatic carbocyclic ring containing from 6 to 10 carbon atoms, which is formed by

removal of two hydrogen atoms. Examples include phenylene (-C₆H₄-), naphthylene (-C₁₀H₆-), etc. The "phenylene" group has the following structure:

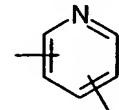


As used herein, the term "heteroarylene" refers to a substituted or unsubstituted 5 to 10 membered aromatic heterocyclic ring formed by removal of two hydrogen atoms. Examples include the heteroarylene groups which correspond to the respective heteroaryl compounds described above, and in particular, include thienylene (-C₄H₂S-), pyridylene (-C₅H₃N-), pyrimidinylene (-C₃H₂N₂-), quinolinylene (-C₉H₅N-), thiazolylene (-C₃HNS-), etc. The "thienylene" group has the following structure:



10

The "pyridylene" group has the following structure:



As used herein, the term "alkoxy" refers to an oxygen radical substituted with an alkyl group. Preferably, the alkoxy group contains from 1 to 6 carbon atoms. A 15 designation such as "C₁-C₄ alkoxy" refers to an alkoxy containing from 1 to 4 carbon atoms. Examples include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy, etc.

As used herein, the term "arylalkyl" refers to an aryl-substituted alkyl group and includes benzyl, bromobenzyl, diphenylmethyl, triphenylmethyl, phenylethyl, 20 diphenylethyl, etc.

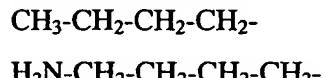
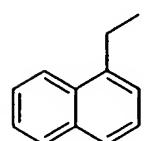
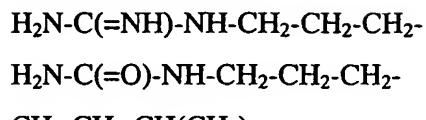
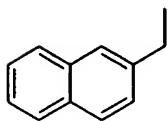
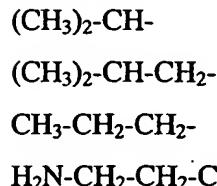
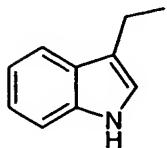
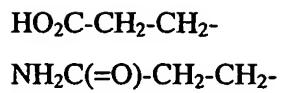
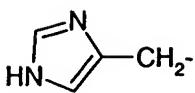
As used herein, "C₅-C₇ monosaccharide" refers to simple sugars of the formula (CH₂O)_n wherein n=5-7. The monosaccharides can be straight-chain or ring systems, and can include a saccharose unit of the formula -CH(OH)-C(=O)-. Examples include erythrose, threose, ribose, arabinose, xylose, lyxose, allose, altroose, glucose, mannose, 25 gulose, idose, galactose, talose, erythulose, ribulose, xyulose, psicose, fructose, sorbose,

tagatose, erythropentulose, threopentulose, glycerotetrulose, glucopyranose, fructofuranose, etc.

As used herein, the term "amino acid" refers to a molecule containing both an amino group and a carboxyl group. Embodiments of amino acids include α -amino, β -amino, γ -amino acids. The α -amino acids have a general formula HOOC-CH(side chain)-NH₂. The amino acids can be in their D, L or racemic configurations. Amino acids include naturally-occurring and non-naturally occurring moieties. The naturally-occurring amino acids include the standard 20 α -amino acids found in proteins, such as glycine, serine, tyrosine, proline, histidine, glutamine, etc. Naturally-occurring amino acids can also include non- α -amino acids (such as β -alanine, γ -aminobutyric acid, homocysteine, etc.), rare (such as 4-hydroxyproline, 5-hydroxylysine, 3-methylhistidine, etc.) and non-protein (such as citrulline, ornithine, canavanine, etc.) amino acids. Non-naturally occurring amino acids are well-known in the art, and include analogs of natural amino acids. See Lehninger, A. L. *Biochemistry*, 2nd ed.; Worth Publishers: New York, 1975; 71-77, the disclosure of which is incorporated herein by reference. Non-naturally occurring amino acids also include α -amino acids wherein the side chains are replaced with synthetic derivatives. Representative side chains of naturally occurring and non-naturally occurring α -amino acids are shown below in Table A.

Table A

CH ₃ -	HS-CH ₂ -
HO-CH ₂ -	HO ₂ C-CH(NH ₂)-CH ₂ -S-S-CH ₂ -
C ₆ H ₅ -CH ₂ -	CH ₃ -CH ₂ -
HO-C ₆ H ₄ -CH ₂ -	CH ₃ -S-CH ₂ -CH ₂ -
	CH ₃ -CH ₂ -S-CH ₂ -CH ₂ -
	HO-CH ₂ -CH ₂ -
	CH ₃ -CH(OH)-
	HO ₂ C-CH ₂ -NHC(=O)-CH ₂ -



As used herein, the term "subject" refers to a warm blooded animal such as a mammal, preferably a human, or a human child, which is afflicted with, or has the potential to be afflicted with one or more diseases and conditions described herein.

As used herein, a "therapeutically effective amount" refers to an amount of a compound of the present invention which is effective in reducing, eliminating, treating or controlling the symptoms of the herein-described diseases and conditions. The term "controlling" is intended to refer to all processes wherein there may be a slowing, interrupting, arresting, or stopping of the progression of the diseases and conditions described herein, but does not necessarily indicate a total elimination of all disease and condition symptoms, and is intended to include prophylactic treatment.

As used herein, the term "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem complications commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. The pharmaceutically acceptable salts include the conventional non-toxic

salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, 5 propionic, succinic, tartaric, citric, glutamic, benzoic, salicylic, toluenesulfonic, oxalic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or 10 base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two. Generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby 15 incorporated by reference.

As used herein, "prodrug" is intended to include any covalently bonded carriers which release the active parent drug according to the compounds of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, 20 bioavailability, manufacturing, etc.), the compounds of the present invention may be delivered in prodrug form. Thus, the present invention contemplates prodrugs of the claimed compounds, compositions containing the same, and methods of delivering the same. Prodrugs of a compound of the present invention may be prepared by modifying functional groups present in the compound in such a way that the modifications are 25 cleaved, either in routine manipulation or *in vivo*, to the parent compound. Accordingly, prodrugs include, for example, compounds of the present invention wherein a hydroxy, amino, or carboxy group is bonded to any group that, when the prodrug is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or carboxylic acid, respectively. Examples include, but are not limited to, acetate, formate and benzoate 30 derivatives of alcohol and amine functional groups; and alkyl, cycloalkyl, aryl, and alkylaryl esters such as methyl, ethyl, cyclopropyl, phenyl, benzyl, and phenethyl esters, etc.

The present invention provides a method of treating diseases and conditions in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound of formula (I), (I-A), (II), or (II-A). For example, the compounds of formula (I), (I-A), (II), or (II-A) can be used in the treatment of sleepiness, 5 preferably sleepiness associated with narcolepsy, promotion of wakefulness, treatment of Parkinson's disease, cerebral ischemia, stroke, sleep apneas, eating disorders, preferably eating disorders associated with a disease, in particular, wherein the disease is *anorexia nervosa*, stimulation of appetite and weight gain, treatment of attention deficit hyperactivity disorder, enhancing function in disorders associated with hypofunctionality 10 of the cerebral cortex, including, but not limited to, depression, schizophrenia, fatigue, in particular, fatigue associated with neurologic disease, such as multiple sclerosis, chronic fatigue syndrome, and improvement of cognitive dysfunction.

The identification of those subjects who are in need of treatment of herein-described diseases and conditions is well within the ability and knowledge of one skilled 15 in the art. A clinician skilled in the art can readily identify, by the use of clinical tests, physical examination and medical/family history, those subjects who are in need of such treatment.

A therapeutically effective amount can be readily determined by the attending 20 diagnostician, as one skilled in the art, by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the therapeutically effective amount, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of subject; its size, age, and general health; the specific disease involved; the degree of involvement or the severity of the disease; the response of the individual subject; the particular compound administered; 25 the mode of administration; the bioavailability characteristic of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

The amount of a compound of formula (I), (I-A), (II), or (II-A) which is required 30 to achieve the desired biological effect will vary depending upon a number of factors, including the dosage of the drug to be administered, the chemical characteristics (e.g., hydrophobicity) of the compounds employed, the potency of the compounds, the type of disease, the diseased state of the patient, and the route of administration. In general

terms, the compounds of this invention may be provided in an aqueous physiological buffer solution containing about 0.1 to 10% w/v compound for parenteral administration. Typical dose ranges are from about 1 $\mu\text{g}/\text{kg}$ to about 1 g/kg of body weight per day; a preferred dose range is from about 0.01 mg/kg to 100 mg/kg of body weight per day. A 5 preferred daily dose for adult humans includes about 25, 50, 100 and 200 mg, and an equivalent dose in a human child. The preferred dosage of drug to be administered is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, and formulation of the compound excipient, and its route of 10 administration.

The compounds of the present invention are capable of being administered in unit dose forms, wherein the term "unit dose" means a single dose which is capable of being administered to a patient, and which can be readily handled and packaged, remaining as a physically and chemically stable unit dose comprising either the active compound itself, 15 or as a pharmaceutically acceptable composition, as described hereinafter. As such, typical daily dose ranges are from about 0.1 to 100 mg/kg of body weight. By way of general guidance, unit doses for humans range from about 0.1 mg to about 1000 mg per day. Preferably the unit dose range is from about 1 to about 500 mg administered one to four times a day, and even more preferably from about 10 mg to about 300 mg, two 20 times a day. In an alternate method of describing an effective dose, a preferred oral unit dose is one that is necessary to achieve a blood serum level of about 0.05 to 20 $\mu\text{g}/\text{ml}$, and more preferably, of about 1 to about 20 $\mu\text{g}/\text{ml}$ in a subject.

Compounds provided herein can be formulated into pharmaceutical compositions by admixture with one or more pharmaceutically acceptable excipients. Such 25 compositions may be prepared for use in oral administration, particularly in the form of tablets or capsules; or parenteral administration, particularly in the form of liquid solutions, suspensions or emulsions; or intranasally, particularly in the form of powders, nasal drops, or aerosols; or dermally, for example, topically or via trans-dermal patches.

The compositions may conveniently be administered in unit dosage form and 30 may be prepared by any of the methods well known in the pharmaceutical art, for example, as described in *Remington: The Science and Practice of Pharmacy*, 20th ed.; Gennaro, A. R., Ed.; Lippincott Williams & Wilkins: Philadelphia, PA, 2000.

Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. Oral compositions will generally include an inert diluent carrier or an edible carrier.

The tablets, pills, powders, capsules, troches and the like can contain one or more of any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, or gum tragacanth; a diluent such as starch or lactose; a disintegrants such as starch and cellulose derivatives; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, or methyl salicylate. Capsules can be in the form of a hard capsule or soft capsule, which are generally made from gelatin blends optionally blended with plasticizers, as well as a starch capsule. In addition, dosage unit forms can contain various other materials that modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or enteric agents. Other oral dosage forms syrup or elixir may contain sweetening agents, preservatives, dyes, colorings, and flavorings. In addition, the active compounds may be incorporated into fast dissolve, modified-release or sustained-release preparations and formulations, and wherein such sustained-release formulations are preferably bi-modal.

Preferred formulations include pharmaceutical compositions in which a compound of the present invention is formulated for oral or parenteral administration, or more preferably those in which a compound of the present invention is formulated as a tablet. Preferred tablets contain lactose, cornstarch, magnesium silicate, croscarmellose sodium, povidone, magnesium stearate, or talc in any combination. It is also an aspect of the present disclosure that a compound of the present invention may be incorporated into a food product or a liquid.

Liquid preparations for administration include sterile aqueous or nonaqueous solutions, suspensions, and emulsions. The liquid compositions may also include binders, buffers, preservatives, chelating agents, sweetening, flavoring and coloring agents, and the like. Nonaqueous solvents include alcohols, propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and organic esters such as ethyl oleate. Aqueous carriers include mixtures of alcohols and water, buffered media, and saline. In particular, biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be useful excipients

to control the release of the active compounds. Intravenous vehicles can include fluid and nutrient replenishers, electrolyte replenishers, such as those based on Ringer's dextrose, and the like. Other potentially useful parenteral delivery systems for these active compounds include ethylene-vinyl acetate copolymer particles, osmotic pumps, 5 implantable infusion systems, and liposomes.

Alternative modes of administration include formulations for inhalation, which include such means as dry powder, aerosol, or drops. They may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or oily solutions for administration in the form of nasal drops, or as a gel to be applied 10 intranasally. Formulations for buccal administration include, for example lozenges or pastilles and may also include a flavored base, such as sucrose or acacia, and other excipients such as glycocholate. Formulations suitable for rectal administration are preferably presented as unit-dose suppositories, with a solid based carrier, such as cocoa butter, and may include a salicylate. Formulations for topical application to the skin 15 preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which can be used include petroleum jelly, lanolin, polyethylene glycols, alcohols, or their combinations. Formulations suitable for transdermal administration can be presented as discrete patches and can be lipophilic emulsions or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive.

20 The compounds of the current invention can be employed as the sole active ingredient in a pharmaceutical composition. Alternatively, they can be used in combination or combined with other pharmaceutical agents associated with other disease states. In particular, the compounds of formula (I), (I-A), (II), or (II-A) can be combined with agents that are useful for the treatment of impaired cognition associated with 25 various disease states including, but not limited to, age, trauma, stress or transient impairment due to chemical imbalance or toxicity, hypersomnia, depression, Alzheimer's Disease, non-Alzheimer's dementias, including Lewy body dementia, vascular dementia and Binswanger's dementia, schizophrenia, and the like. The present invention would encompass, therefore, combinations of the compounds of the current invention with 30 eburnane analogs, heterocyclic inducers of tyrosine hydroxylase, 3,4-diphenyl chromans, tacrine metabolites, aza-cyclic compounds, polyamine compounds, or thiamine; nonanticholinergic antidepressants such as benzodiazepines; phenothiazines aliphatic

such as chlorpromazine; piperidines such as thioridazine; piperazines such as trifluoperazine, fluphenazine and perphenazine; dibenzoxazepines such as loxapine; dihydroindolones such as molindone; thioxanthenes such as thiothixene; butyrophophenes such as haloperidol; diphenylbutyl-piperidines such as pimozide; dibenzodiazepine such 5 as clozapine; benzisoxazole such as risperidone; thienobenzodiazepine such as olanzapine; dibenzothiazepine such as quetiapine; imidazolidinone such as sertindole, benzisothiazolyl-piperazine such as ziprasidone, and the like.

Synthesis

The compounds of the present invention may be prepared in a number of ways 10 well known to those skilled in the art. The compounds can be synthesized, for example, by the methods described below, or variations thereon as appreciated by the skilled artisan. The appropriate modifications and substitutions being readily apparent and well known or readily obtainable from the scientific literature to those skilled in the art.

It will be appreciated that the compounds of the present invention may contain 15 one or more asymmetrically substituted carbon atoms, and may be isolated in optically active or racemic forms. Thus, all chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. It is well known in the art how to prepare and isolate such optically active forms. For example, mixtures of stereoisomers may be 20 separated by standard techniques including, but not limited to, resolution of racemic forms, normal, reverse-phase, and chiral chromatography, preferential salt formation, recrystallization, and the like, or by chiral synthesis either from chiral starting materials or by deliberate synthesis of target chiral centers.

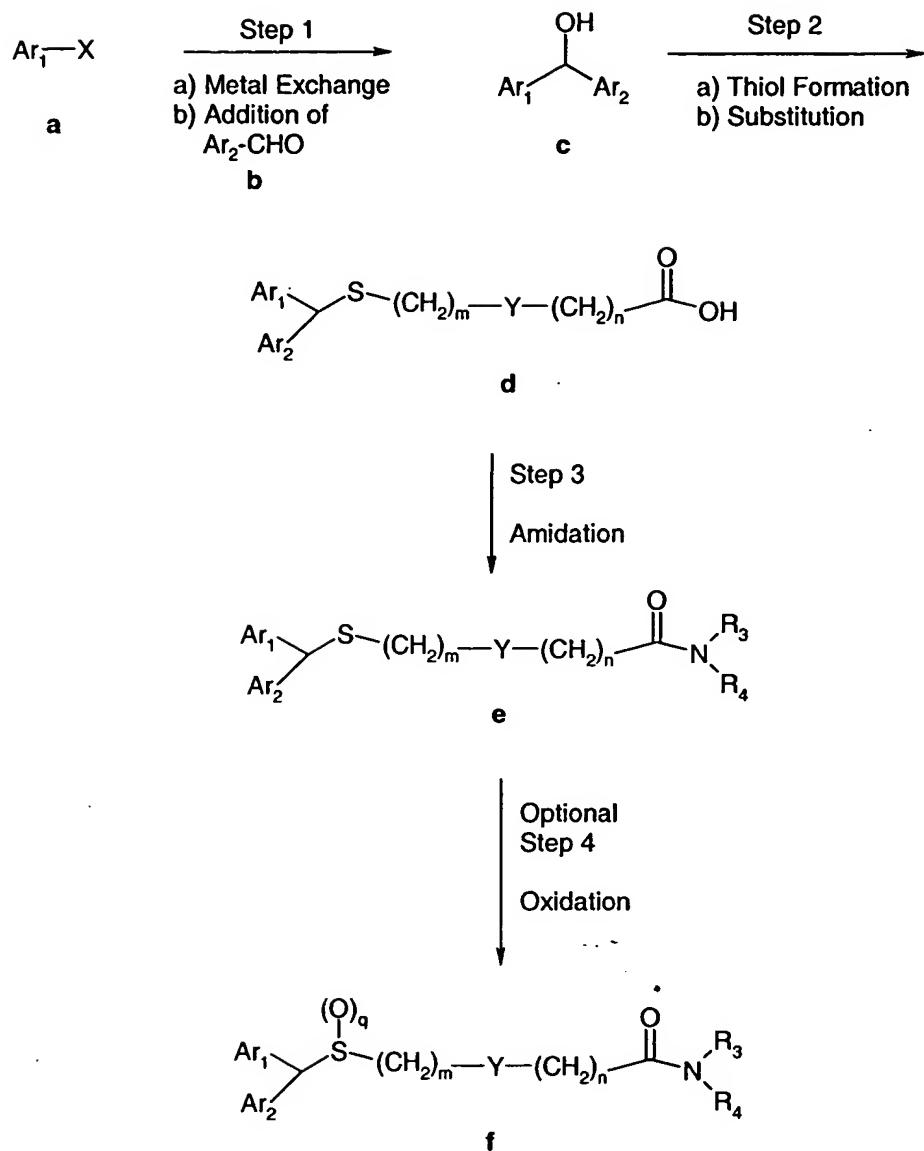
As will be readily understood, functional groups present on the compounds of the 25 present invention may contain protecting groups during the course of synthesis. For example, the amino acid side chain substituents of the compounds of formula (I), (I-A), (II), or (II-A) can be substituted with protecting groups such as benzyloxycarbonyl or t-butoxycarbonyl groups. Protecting groups are known per se as chemical functional groups that can be selectively appended to and removed from functionalities, such as 30 hydroxyl groups and carboxyl groups. These groups are present in a chemical compound to render such functionality inert to chemical reaction conditions to which the compound

is exposed. Any of a variety of protecting groups may be employed with the present invention. Preferred protecting groups include the benzyloxycarbonyl ("Cbz") group, the *tert*-butyloxycarbonyl ("Boc") group, and the tosyl (p-toluenesulfonyl, "Tos") group. Other preferred protecting groups according to the invention may be found in Greene,

5 T.W. and Wuts, P.G.M., *Protective Groups in Organic Synthesis* 2d. Ed., Wiley & Sons, 1991.

Compounds of the present invention may be prepared as outlined in the following schemes. The reagents and starting materials are commercially available, or readily synthesized by well-known techniques by one of ordinary skill in the arts. All 10 substituents, unless otherwise indicated, are as previously defined.

A general synthetic procedure is set forth in **Scheme A** for preparing the compounds of formula (I) [wherein Y=C(R₁)(R₂) and m, n=0] or (I-A):

Scheme A**Scheme A, step 1:** Synthesis of compounds of general structure **c**:

In step 1a, the appropriate aryl halide **a** undergoes a metal exchange reaction with an organometallic compound to give the corresponding metallocaryl compound. For example, an appropriate haloaromatic or haloheteroaromatic (compound **a**) is reacted with an appropriate alkyl lithium compound in an aprotic solvent at a temperature -78°C . An appropriate haloaromatic or haloheteroaromatic compound is one where Ar_1 is as

defined in the final product. An appropriate alkyl lithium compound is one that effects a metal-halogen exchange.

5 In step 1b, an appropriate aryl aldehyde **b** is added to the previously formed metalloaryl compound to give desired di-aryl alcohol **c**. For example, an appropriate aromatic aldehyde or heteroaromatic aldehyde (compound **b**) in an aprotic solvent is added to reaction product of step 1a. An appropriate heteroaromatic aldehyde is one where Ar₂ is as defined in the final product. Upon completion, the reaction mixture is quenched by an appropriate quenching agent and the product, compound **c**, is isolated by conventional methods commonly employed by those skilled in the art.

10 For example, a cooled (-70 °C to -78 °C) solution of an appropriate haloaromatic or haloheteroaromatic (compound **a**) in dry ether is reacted with n-butyllithium (1.1 eqv). After stirring for an additional period of time to allow the completion of halogen-metal exchange reaction, the next reactant, an appropriate heteroaromatic aldehyde (compound **b**) in ether is slowly be added to the reaction flask. Stirring is continued for an additional 15 2-3 h at the low temperature. The cooling bath is removed and the reaction mixture is slowly allowed to come to ambient temperature, followed by quenching, preferably by a saturated NH₄Cl solution. The mixture is extracted into an organic solvent (ether or ethyl acetate). The organic layer is washed with brine, dried (MgSO₄ or Na₂SO₄) and concentrated to give a crude product. Purification is achieved by employing known 20 purification techniques (preferably by column chromatography and/or recrystallization) to provide pure compounds **c**. The method is an adaptation from a procedure previously described by Gronowitz, S.; Eriksson, B. *Arkiv Kemi* 1963, 335, incorporated herein by reference in its entirety. Alternatively, this class of compounds wherein Ar₁ is the same as Ar₂ may be generated by treatment of two equivalents of an appropriate 25 haloheteroaromatic with two equivalents of n-butyllithium, followed by one equivalent of ethyl formate as described by Nenajdenko, V. G.; Baraznenok, I. L.; Balenkova, E. S. *J. Org. Chem.* 1998, 6132, incorporated herein by reference in its entirety.

Scheme A, step 2: Synthesis of compounds of general structure **d:**

30 In step 2a, the alcohol moiety of compound **c** is converted to the corresponding thiol. The thiol, in step 2b, undergoes a substitution reaction with an appropriate halogen-substituted alkylcarboxylic acid of structure Br-(CH₂)_m-Y-(CH₂)_n-COOH, to

generate compound **d**. For example, di-aryl alcohol **c** is reacted with thiourea in presence of an acid to convert it to a thiouronium moiety that is subsequently hydrolyzed in the presence of an alkaline base and reacted with the appropriate halogen-substituted alkylcarboxylic acid to generate compound **d** (step 2b). An appropriate acid derivative is 5 one in which m, n, Y are as defined in the final product.

For example, in step 2a, an appropriate amount of thiourea is taken into 48% HBr and water. The mixture is warmed (preferably to 60 – 70 °C), followed by addition of compound **c**. The temperature of the reaction mixture is elevated (preferably to 90–95 °C) and the stirring is continued for an additional period of time for completion of the 10 reaction. The reaction mixture is cooled to room temperature (in some cases, an ice-bath might be needed) and the precipitated solid should be filtered and thoroughly washed with water.

In step 2b, the wet solid from the previous step is taken into additional water and treated with an aqueous base, preferably sodium hydroxide solution. The mixture is 15 warmed (preferably to 70 – 80 °C, but in some cases a higher temperature might be needed) and to it an appropriate amount of halogen-substituted alkylcarboxylic acid derivative in water (or in some cases, an alcoholic solvent) is added. The reaction mixture is maintained at an elevated temperature (preferably 100 – 110 °C) for an appropriate period of time, cooled, taken into water and washed with an organic solvent 20 (preferably ether). The basic aqueous layer is acidified with an inorganic acid solution (e.g. aqueous HCl solution). The aqueous (acidic) solution is then extracted several times into an organic solvent (e.g. ether or ethyl acetate). The combined organic layer is washed with brine, dried ($MgSO_4$ or Na_2SO_4) and concentrated to give the crude product that may be used directly in the next step. However, purification could be achieved by 25 employing known purification techniques (e.g. recrystallization) to provide pure compound **d**.

The method is an adaptation from a procedure previously described in U.S. Pat. No. 4,177,290, incorporated by reference herein in its entirety.

Scheme A, step 3: Synthesis of compounds of general structure **e:**

30 In step 3a, the carboxylic acid is converted into appropriate acid derivative, which is then reacted with an appropriate amine to give compound **e**. For example in step 3a,

compound **d** can be converted to the corresponding acid chloride, or the corresponding activated ester. The acid chloride can be obtained by reacting compound **d** with thionyl chloride in an aromatic hydrocarbon solvent in refluxing condition. Alternatively, the activated ester can be obtained by use of various agents known in the art, such as 2-(1H-5 Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate ("TBTU"), *N*-methylmorpholine ("NMM") and dimethyl formamide ("DMF"). In step 3b, the product of step 3a is reacted with an appropriate amine of structure NHR_3R_4 to give the desired compound **e**. An appropriate amine is one which correlates to R_3 and R_4 as defined in the final product.

10 For example, a solution of an appropriate carboxylic acid (compound **d**) in either benzene or toluene is brought to reflux temperature and to it is slowly added an appropriate amount of thionyl chloride. The mixture is refluxed until the disappearance of starting material (as evidenced by analytical techniques), cooled and solvent removed. The resulting residue is taken into an appropriate organic solvent (preferably tetrahydrofuran or methylene chloride) and treated with ammonia gas (or 28% aqueous ammonia hydroxide solution) or an appropriate amine. The reaction mixture is then partitioned between water and an organic solvent (preferably ethyl acetate). The separated organic layer is washed with water, dilute acid, dilute base and brine, dried over a drying agent (e.g. MgSO_4 or Na_2SO_4) and concentrated to give the crude product 15 that may be purified by column chromatography and/or recrystallization to produce compound **e**.

20

Scheme A, optional step 4: Synthesis of compounds of general structure **f:**

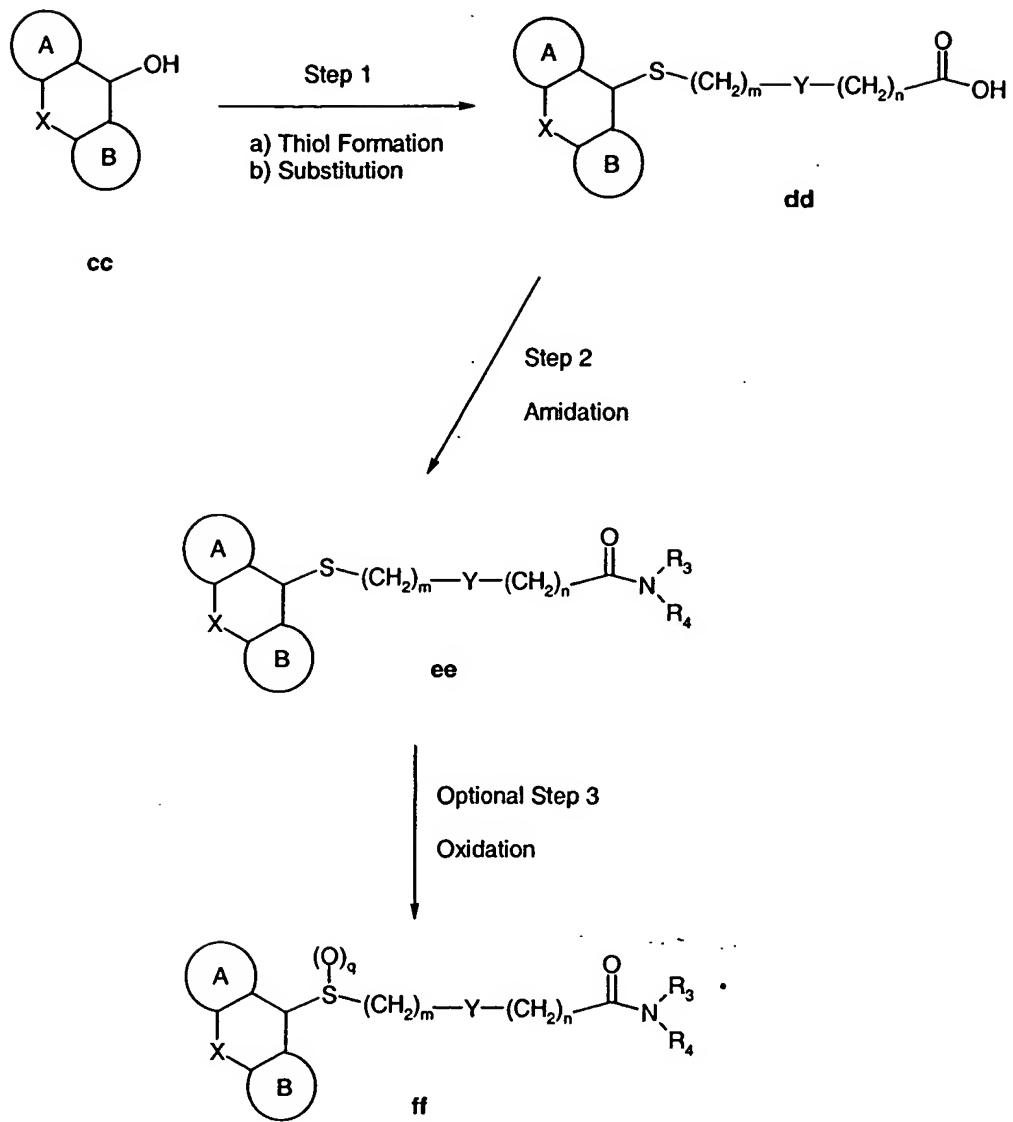
Compounds of structure **e** may optionally be oxidized to generate compounds of structure **f**. Thus, compound **f** is prepared by reacting compound **e** in an appropriate 25 solvent with an appropriate oxidizing agent. An appropriate oxidizing agent is one that oxidizes the sulfide group of compound **e**. The corresponding product is isolated and purified by methods well known in the art.

For example, to a cooled (-15 °C to -25 °C) solution of compound **e** in an organic solvent (preferably methylene chloride or chloroform), an appropriate oxidizing agent 30 (e.g. *m*-chloroperoxybenzoic acid ["*m*-CPBA"], 1 equivalent) in the same solvent is slowly added. Stirring is continued at low temperature until the disappearance of the

starting material, as evidenced by various analytical techniques. The reaction mixture is then thoroughly washed with a saturated sodium bicarbonate solution, water and brine, respectively, dried over a drying agent (e.g. MgSO₄ or Na₂SO₄) and concentrated. The desired product (compound f) is purified, if needed, by employing known purification techniques (preferably by column chromatography and/or recrystallization). In some cases, the oxidation is performed by employing 50% H₂O₂ in glacial acetic acid solvent.

5 A general synthetic procedure is set forth in **Scheme B** for preparing the compounds of formula (II) [wherein ring A is phenylene; Y=C(R₁)(R₂) and m, n=0] and (II-A):

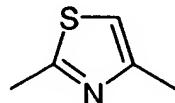
Scheme B



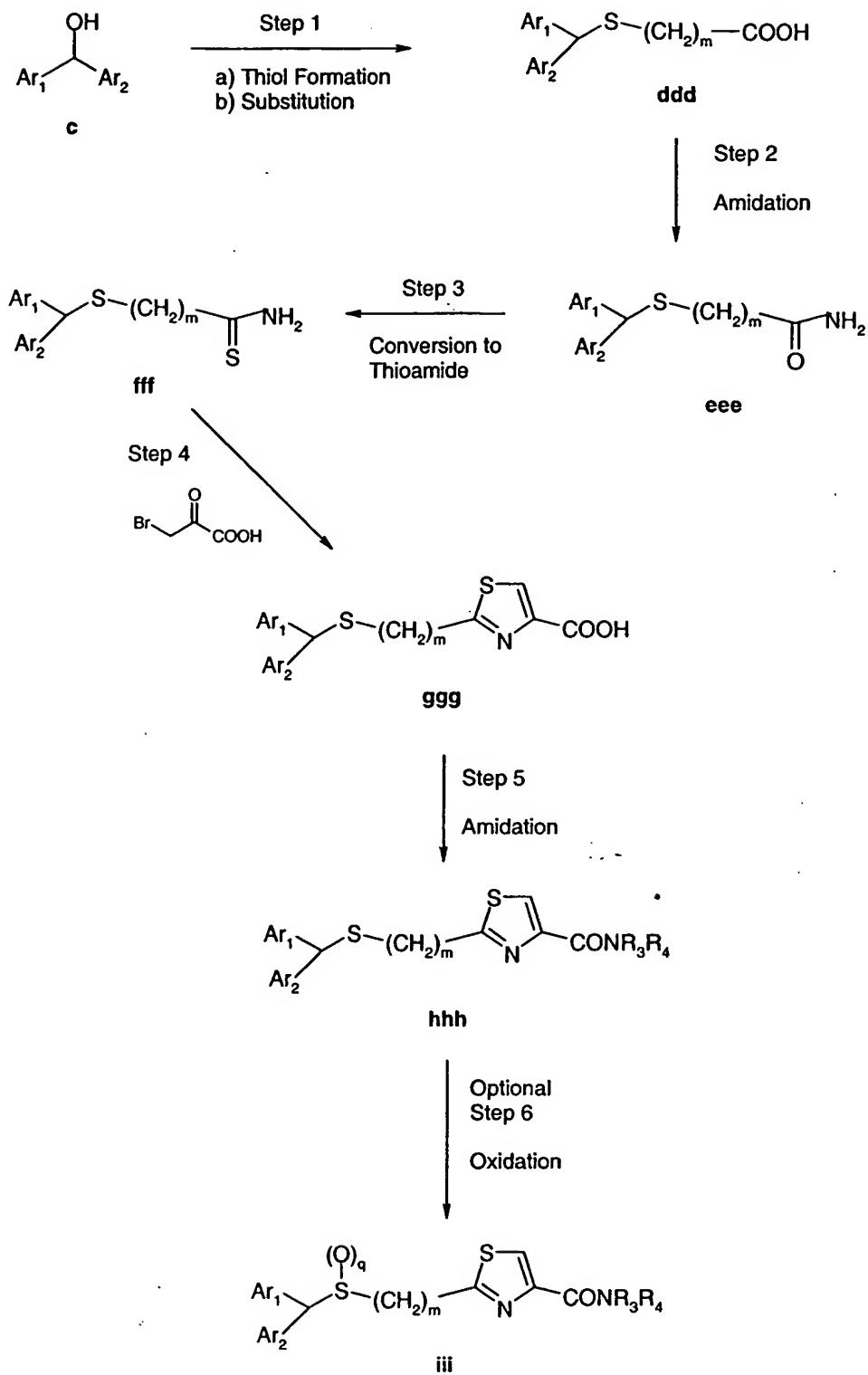
Scheme B, steps 1, 2, and 3: Synthesis of compounds of general structure **dd**, **ee** and **ff**.

The synthetic steps in **Scheme B** involve the same multistep general method described in **Scheme A**, wherein **Scheme B**, steps 1-3 corresponds to **Scheme A**, steps 2-4, respectively.

5 A general synthetic procedure is set forth in **Scheme C** for preparing the compounds of formula (I-A), wherein $n=0$ and Y is



Scheme C



Scheme C, steps 1 and 2: Synthesis of compounds of general structure ddd and eee.

The synthetic steps in **Scheme C**, steps 1 and 2 involve the same multistep general method described in **Scheme A**, steps 2-3, respectively to give compounds of structure **eee**.

5 **Scheme C, step 3: Synthesis of compounds of general structure fff.**

The amide moiety in compound **eee** is converted to corresponding thioamide moiety **fff** with an appropriate sulfur-transfer reagent. For example, a mixture of compound **eee** and Lawesson's reagent (1.05 eqv) in a suitable solvent (dimethoxyethane or tetrahydrofuran) is heated to reflux until the disappearance of the starting material.

10 After cooling, the desired product (compound **fff**) is obtained by employing known purification techniques (preferably by column chromatography and/or recrystallization).

Scheme C, step 4: Synthesis of compounds of general structure ggg.

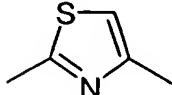
The thioamide moiety in compound **fff** is cyclized to the corresponding thiazole moiety. For example, a mixture of compound **fff** and an appropriate bromomethyl

15 ketone (1.1 eqv) in a suitable solvent (e.g. ethanol) is heated to reflux until the disappearance of the starting material. After cooling, the desired product (compound **ggg**) is obtained by employing known purification techniques (preferably by column chromatography and/or recrystallization).

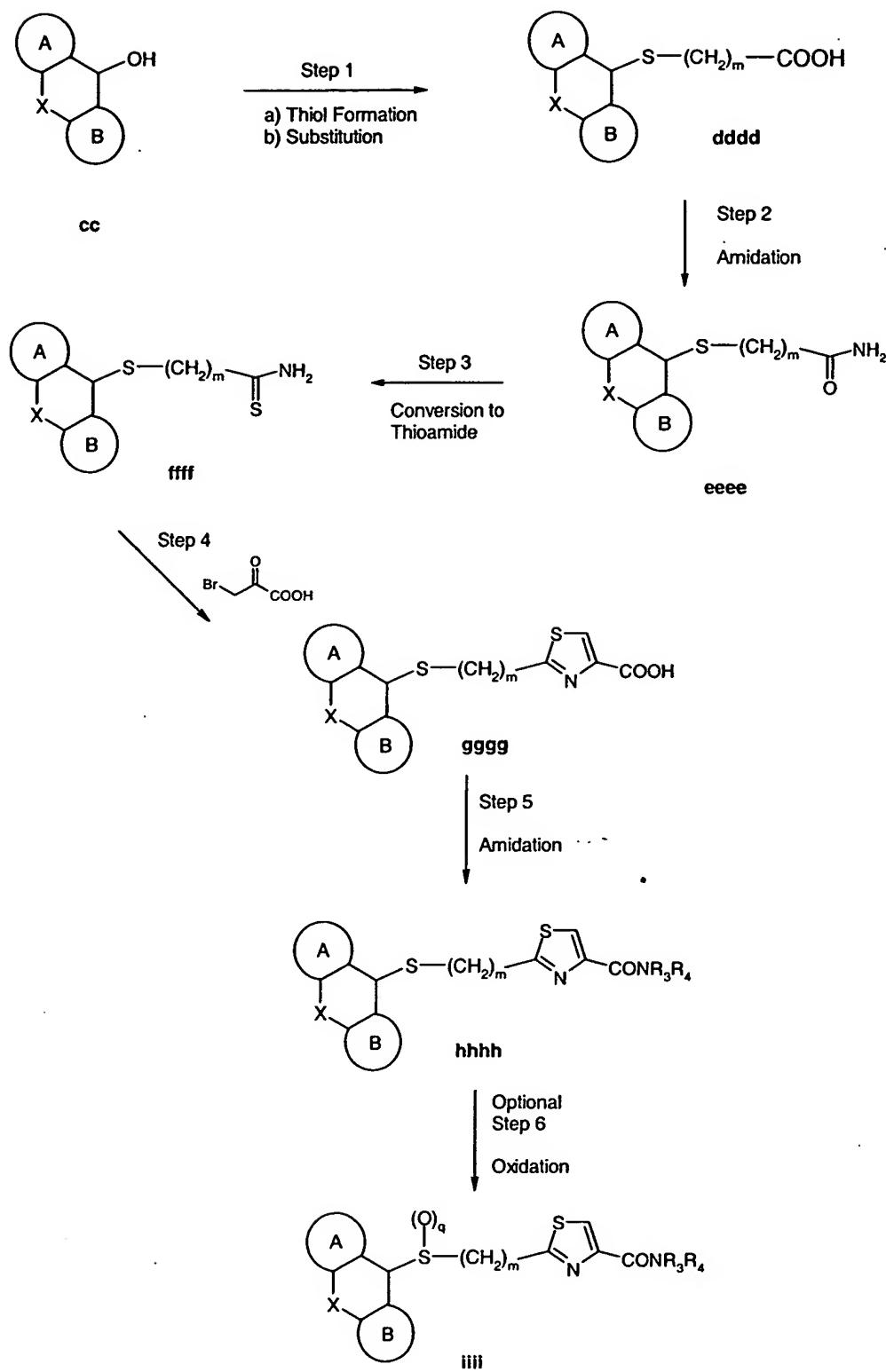
Scheme C, steps 5-6: Synthesis of compounds of general structure hhh and iii.

20 The synthetic steps in **Scheme C**, steps 5 and 6 involve the same multistep general method described in **Scheme A**, steps 3 and 4, respectively to give compounds of structure **hhh** and **iii**.

A general synthetic procedure is set forth in **Scheme D** for preparing the compounds of formula (II-A), wherein n=0 and Y is



Scheme D

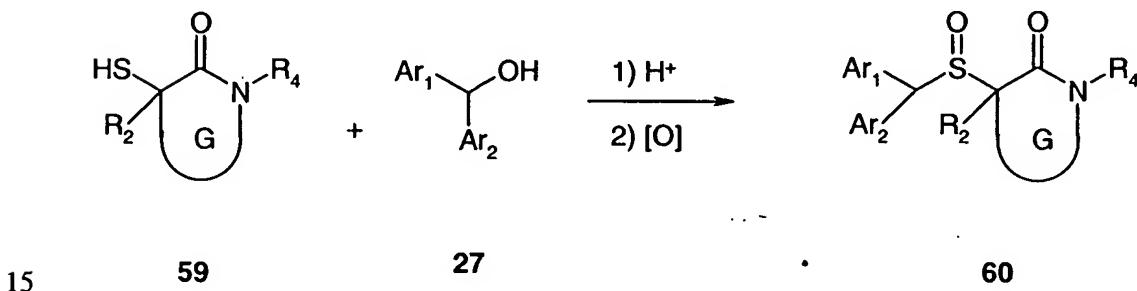


Scheme D, steps 1-6: Synthesis of compounds of general structure **hhhh and **iiii**.**

The synthetic steps in **Scheme D** involve the same multistep general method described in **Scheme C** to give compounds of structure **hhhh** and optionally, **iiii**.

5 A synthetic procedure is set forth in Reaction Scheme E for preparing compounds of formula (I) or (I-A) wherein R₁ or R₂ can be taken together with either R₃ or R₄ to form a 3-7 member heterocyclic ring. The subsequently formed ring is represented in Scheme E by "G". In the present scheme, R₁ is taken together with R₃ to form heterocyclic ring "G". It is understood that R₁ may be also be taken with R₄ to form ring "G", or R₂ may be also be taken with R₃ to form ring "G", or R₂ may be also be taken with R₄ to form ring "G". The reagents and starting materials are commercially available, or readily synthesized by well-known techniques by one of ordinary skill in the arts. In Reaction Scheme E, all substituents, unless otherwise indicated, are as previously defined.

Scheme E



Scheme E, steps 1 and 2: Synthesis of compounds of general structure **60**, containing compounds of formula (I) wherein either R_1 or R_2 are taken together with either R_3 or R_4 to form a 3-7 member heterocyclic ring “G”.

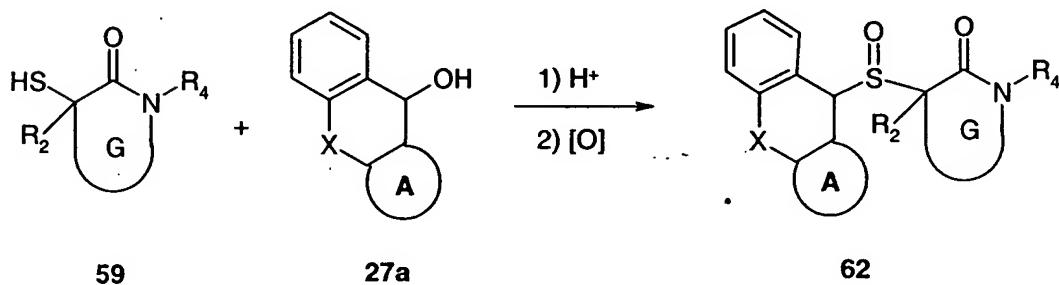
In the first step, an appropriate mercaptolactam **59** is reacted with an appropriate diarylmethanol, compound **27**, in the presence of a weak acid, in order to affect nucleophilic displacement at the methanol carbon to form the corresponding thioether. The appropriate mercaptolactam **59** and appropriate diaryl- or diheteroarylmethanol, **27** are ones in which Ar₁, Ar₂, R₂ and R₄ are as defined in the final product.

In the second step, the thioether formed in the first step is optionally oxidized with an appropriate oxidizing agent to provide compound **60**. An appropriate oxidizing agent is one that oxidizes the thioether to its corresponding sulfoxide or sulfone.

A synthetic procedure is set forth in Reaction Scheme F for preparing compounds of formula (II-A), wherein R₁ or R₂ can be taken together with either R₃ or R₄ to form a 3-7 member heterocyclic ring. A similar procedure may be utilized to prepare the corresponding compounds of formula (II-A). The subsequently formed ring is represented in Scheme E by "G". In the present scheme, R₁ is taken together with R₃ to form heterocyclic ring "G". It is understood that R₁ may be also be taken with R₄ to form ring "G", or R₂ may be also be taken with R₃ to form ring "G", or R₂ may be also be taken with R₄ to form ring "G". The reagents and starting materials are commercially available, or readily synthesized by well-known techniques by one of ordinary skill in the arts. In Reaction Scheme F, all substituents, unless otherwise indicated, are as previously defined.

15

Scheme F



Scheme F, steps 1 and 2: Synthesis of compounds of general structure 62, containing compounds of formula (II-A) wherein either R₁ or R₂ are taken together with either R₃ or R₄ to form a 3-7 member heterocyclic ring “G”.

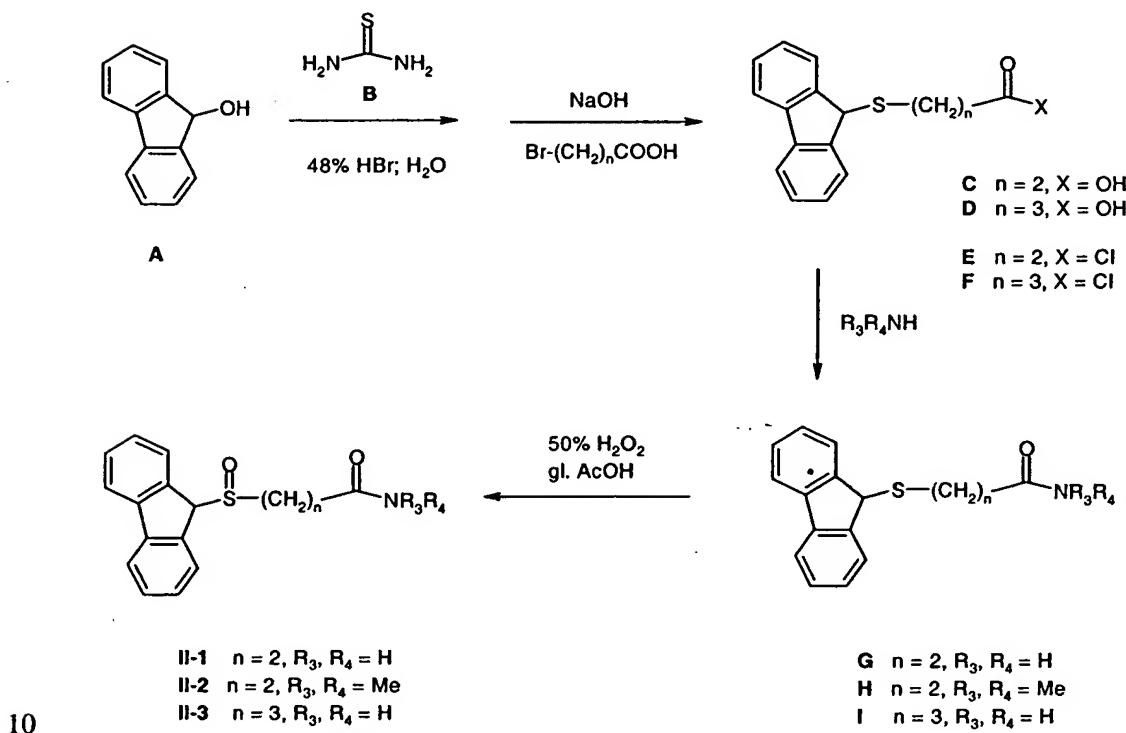
20 In the first step, an appropriate mercaptolactam **59** is reacted with an appropriate diaryl- or diheteroarylmethanol, **27a**, in the presence of a weak acid, in order to affect nucleophilic displacement at the methanol carbon to form the corresponding thioether. The appropriate mercaptolactam **61** and appropriate diaryl- or diheteroarylmethanol, **27a** are ones in which A, X, R₂ and R₄ are as defined in the final product.

In the second step, the thioether formed in the first step is optionally oxidized with an appropriate oxidizing agent to provide compound **62**. An appropriate oxidizing agent is one that oxidizes the thioether to its corresponding sulfoxide or sulfone.

Examples

5 Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments. These examples are given for illustration of the invention and are not intended to be limiting thereof. The following Examples 1-6 were synthesized according to Scheme 1.

Scheme 1



Preparation of compound C:

To a vigorously stirred mixture of thiourea (compound **B**, 5 g, 0.066 mol), 48% HBr (30 mL) and water (5 mL) at 70-75 °C was added 9-hydroxyfluorene (compound **A**, 9.28 g, 0.051 mol) in small portions, followed by additional amount of water (30 mL).

The reaction mixture was then heated to 100-105 °C (bath temperature), maintained there for another 30 min and cooled to room temperature. The precipitated solid was filtered, washed with water and ether, successively and dried under vacuum to generate 14 g of the corresponding thiuronium salt that was used in the next step without any further 5 purification.

To a vigorously stirred mixture of the above-mentioned thiuronium salt (10.47 g,) in 10 N NaOH (10.26 mL) and water (25 mL) at 60-65 °C was slowly added 3-bromopropionic acid (5.24 g, 0.034 mol) in water (20 mL). The reaction mixture was then heated to 105-110 °C (bath temperature), maintained there for another 30 min, 10 cooled to room temperature, diluted with water (25 mL), and washed with ether (3 x 50 mL). The basic aqueous layer was acidified (pH 2~3) with conc. HCl and extracted into ethyl acetate (3 x 100 mL). The combined organic layer was dried (MgSO_4) and concentrated to generate 7.80 g of compound **C** that was used in the next step without any further purification; $^1\text{H-NMR}$ (CDCl_3) δ 7.80 (m, 4H), 7.30 (m, 4H), 4.90 (s, 1H), 15 2.10 (m, 4H).

Preparation of compound **D**:

This compound was prepared from compound **A**, following the same procedure as described above for the synthesis of compound **D**, except that 4-bromobutyric acid was used in place of 3-bromopropionic acid in the alkylation step; $^1\text{H-NMR}$ (CDCl_3) δ 20 7.70 (m, 4H), 7.40 (m, 4H), 4.80 (s, 1H), 2.20 (t, 2H), 2.00 (t, 2H), 1.40 (m, 2H).

Preparation of compound **E**:

To a refluxing solution of compound **C** (7.8 g, 0.029 mol) in benzene (40 mL) was slowly added thionyl chloride (5.3 mL). The mixture was refluxed for another 2 h, cooled, filtered and concentrated under reduced pressure to generate 8 g of compound **E** 25 that was immediately taken into next step without any further purification.

Preparation of compound **F**:

This compound was prepared from compound **D**, following the same procedure as described above for the synthesis of compound **E** from compound **C**.

Example 1: Synthesis of compound G.

Compound E (8 g) from previous step was dissolved in methylene chloride (20 mL) and added to a vigorously stirred, cooled (0 °C) 28% NH₄OH solution (50 mL). The ice-bath was removed and stirring was continued for another hour. The reaction 5 mixture was diluted with water (30 mL) and extracted into methylene chloride (2 x 30 mL). The combined organic layer was washed with water (2 x 20 mL), 3% NaHCO₃ solution (2 x 30 mL), brine (1 x 30 mL), dried (Na₂SO₄) and concentrated to give a residue that was triturated with ether to generate 6.30 g of compound G; ¹H-NMR (DMSO-d₆) δ 7.90 (d, 2H), 7.70 (d, 2H), 7.40 (m, 4H), 7.30 (broad, 1H), 6.80 (broad, 10 1H), 5.20 (s, 1H), 2.30 (t, 2H), 2.10 (t, 2H).

Example 2: Synthesis of compound H.

This compound was prepared from compound E, following the same procedure as described above for the synthesis of compound G, except that dimethylamine was used in place of 28% NH₄OH in the amination step; ¹H-NMR (DMSO-d₆) δ 7.90 (d, 2H), 15 7.60 (d, 2H), 7.40 (m, 4H), 5.20 (s, 1H), 2.70 (2 singlets, 6H), 2.20 (m, 4H).

Example 3: Synthesis of compound I.

This compound was prepared from compound F, following the same procedure as described above for the synthesis of compound G from compound E; ¹H-NMR (DMSO-d₆) δ 7.80 (d, 2H), 7.60 (d, 2H), 7.40 (m, 4H), 7.10 (broad, 1H), 6.70 (broad, 20 1H), 5.10 (s, 1H), 2.10 (t, 2H), 2.00 (t, 2H), 1.50 (m, 2H).

Example 4: Synthesis of compound II-1.

To a solution of compound G (5.15 g, 0.019 mol) in glacial acetic acid (20 mL) at room temperature was slowly added 50% H₂O₂ (1.2 eqv). The mixture was stirred for 1 h, poured into ice-water and filtered. The precipitated solid was thoroughly washed with 25 water, followed by ether and dried under high vacuum to generate 4.42 g of compound II-1; white solid; mp 163-164 °C; R, 7.57 min. ¹H-NMR (DMSO-d₆) δ 8.10-7.50 (a series of m, 8H), 7.40 (broad, 1H), 6.90 (broad, 1H), 5.70 (s, 1H), 2.30 (m, 4H).

Example 5: Synthesis of compound II-2.

This compound was prepared from compound H, following the same procedure as described above for the synthesis of compound II-1 from compound G; white solid; mp 110-112 °C; R, 8.64 min. $^1\text{H-NMR}$ (DMSO-d₆) δ 8.00 (t, 2H), 7.70 (d, 1H), 7.60 (d, 1H), 7.50 (m, 2H), 7.40 (q, 2H), 5.60 (s, 1H), 2.80 (s, 3H), 2.70 (s, 3H), 2.60-2.20 (a series of m, 4H).

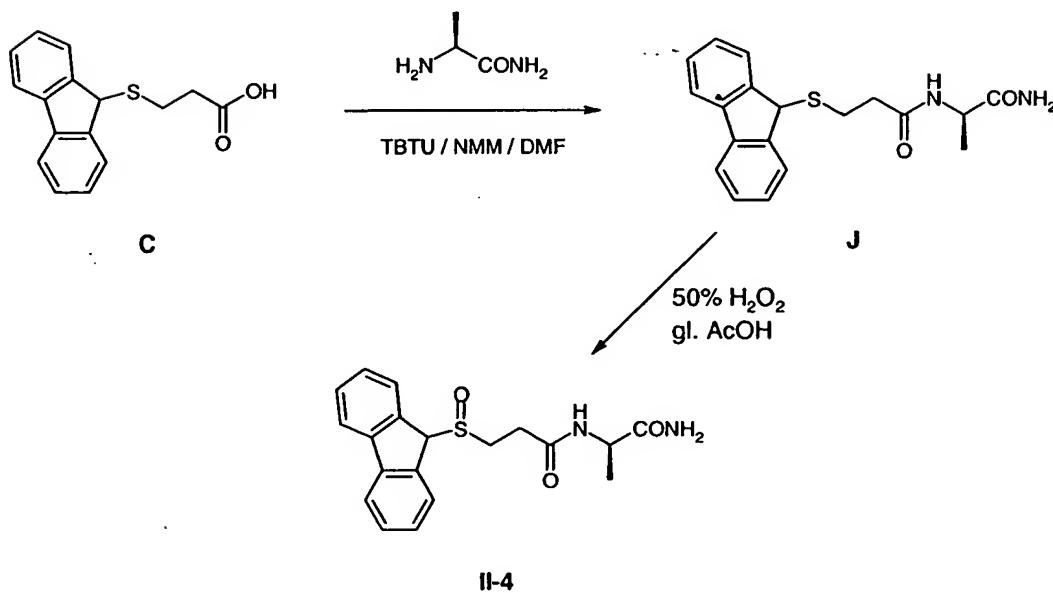
Example 6: Synthesis of compound II-3.

This compound was prepared from compound I, following the same procedure as described above for the synthesis of compound II-1 from compound G; white solid; mp 161-162 °C; R, 7.61 min. $^1\text{H-NMR}$ (DMSO-d₆) δ 8.20-7.60 (a series of m, 8H), 7.40 (broad, 1H), 6.90 (broad, 1H), 5.80 (s, 1H), 2.30 (m, 4H), 1.80 (m, 2H).

The following Examples 7-8 were synthesized according to Scheme 2.

15

Scheme 2



Example 7: Synthesis of compound J.

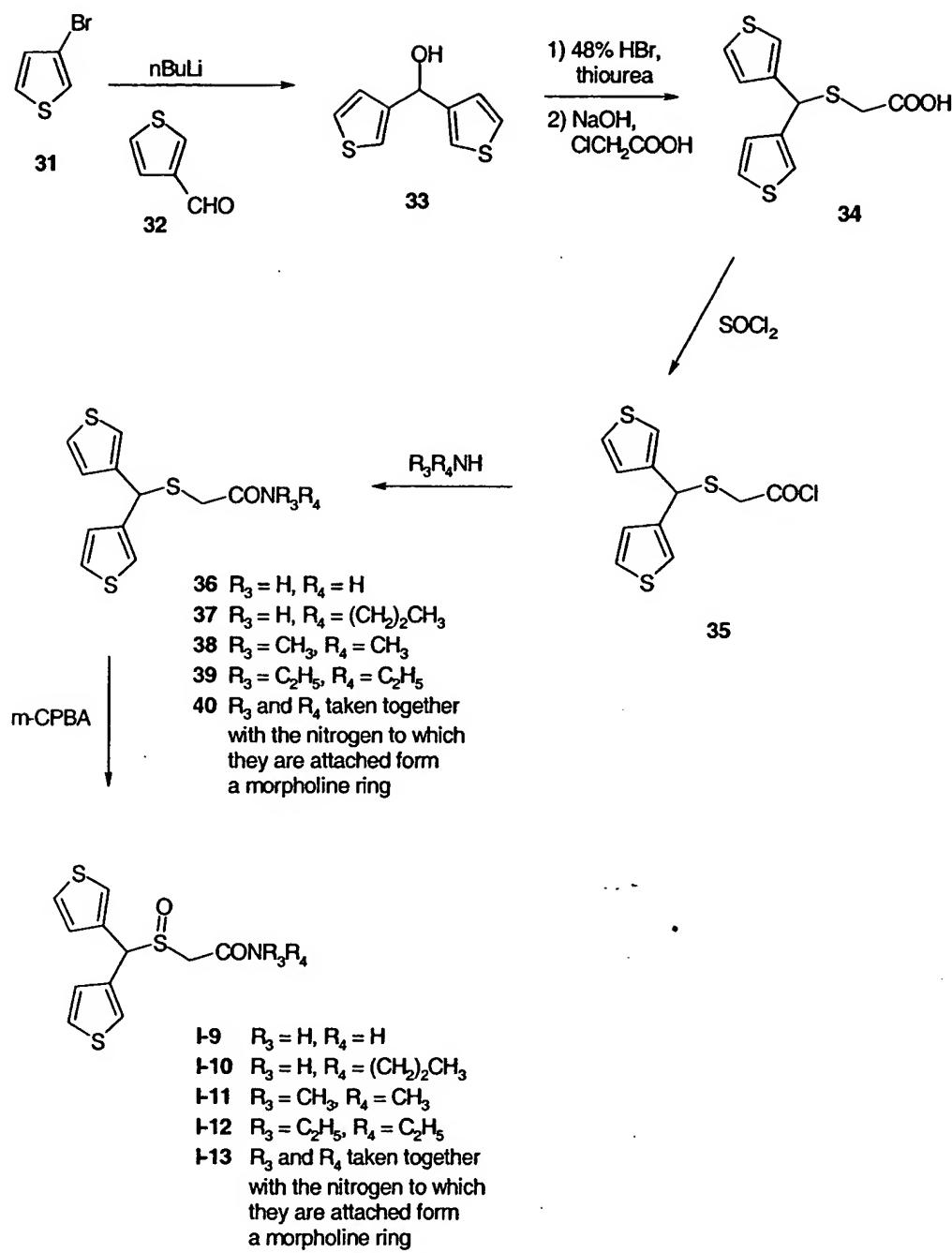
To a stirred solution of compound C (1.9 g, 0.007 mol) in dry DMF (20 mL) at 0 °C was added *N*-methylmorpholine ("NMM") (1.92 mL), followed by 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate ("TBTU") (3.38 g. 5 0.0105 mol). The mixture was stirred for 10 min and to it added (L)-alaninamide (as hydrochloride salt) (1.3 g, 0.0105 mol) in dry DMF (5 mL). The cooling bath was removed and the mixture was stirred for another 2 h. It was then poured into cold water (25 mL) and extracted into ethyl acetate (3 x 50 mL). The combined organic layer was washed with water, 2% citric acid, 3% sodium bicarbonate, water and brine, 10 successively. Drying (MgSO_4) and solvent evaporation produced a residue that on trituration with cold ether generated 1.93 g of compound J; $^1\text{H-NMR}$ (DMSO-d_6) δ 7.70 (m, 3H), 7.50 (d, 2H), 7.20 (m, 4H), 7.10 (broad, 1H), 6.80 (broad, 1H), 5.00 (s, 1H), 4.00 (m, 1H), 2.10 (m, 2H), 2.00 (m, 2H), 0.90 (d, 3H).

Example 8: Synthesis of compound II-4.

15 This compound was prepared from compound J, following the same procedure as described above for the synthesis of compound II-1 from compound G (Scheme 1); white solid (diastereomeric mixture); R_f 7.16 min. $^1\text{H-NMR}$ (DMSO-d_6) δ 8.30 (2 overlapping d, 1H), 8.20–7.60 (a series of m, 8H), 7.50 (d, 1H), 7.10 (d, 1H), 5.80 (s, 1H), 4.20 (m 1H), 2.60-2.40 (2 sets of m, 4H), 1.30 (2 overlapping d, 3H).

20 The following Examples 9-18 were synthesized according to Scheme 3.

Scheme 3



Preparation of compound 33:

Scheme 3, step 1: In step 1a, 3-bromothiophene (10.22 g)(compound 31) in dry ether at a temperature -70° C to -78° C was reacted with n-butyllithium (25 ml of 2.5 M, 1.1 equivalents). After stirring for an additional period of time to allow for the completion of the halogen-metal exchange reaction, 3-thiophenecarboxaldehyde (6.39 g)(compound 32) in ether was slowly added to the reaction flask. Stirring was continued for an additional 2-3 h at the low temperature. The cooling bath was removed and the reaction mixture was slowly allowed to come to ambient temperature, followed by quenching, preferably by 50% aqueous NH₄Cl solution. The mixture was extracted into an organic solvent (ether or ethyl acetate). The organic layer was washed with brine, dried (MgSO₄ or Na₂SO₄) and concentrated to give a crude product. Purification may be achieved by employing known purification techniques (preferably by column chromatography and/or recrystallization) to provide pure compound 33; ¹H-NMR (CDCl₃) δ 7.40 (d, 2H), 7.30 (s, 2H), 7.10 (d, 2H), 6.00 (d, 1H), 2.20 (d, 2H). The method was an adaptation from a procedure previously described by Gronowitz, S.; Eriksson, B. *Arkiv Kemi* 1963, 335, incorporated herein by reference in its entirety.

Preparation of compound 34:

Scheme 3, step 2: In the first step, thiourea (5 g, 1.3 equivalents) was taken into 48% HBr and water. The mixture was warmed (preferably to 60° – 70° C), followed by addition of compound 33 (10 g). The temperature of the reaction mixture was elevated (preferably to 90° – 95° C) and stirring was continued for an additional period of time for completion of the reaction. The reaction mixture was then cooled to room temperature (in some cases, an ice-bath might be needed) and the precipitated solid was filtered and thoroughly washed with water.

The wet solid was then taken into additional water and treated with an aqueous base, preferably sodium hydroxide solution. The mixture was warmed (preferably to 70° – 80° C, but in some cases, a higher temperature might be needed) and to it chloroacetic acid (4.8 g, 1.1 equivalents) in water was added. The reaction mixture was maintained at an elevated temperature (preferably 100° – 110° C) for an appropriate period of time, cooled, taken into water and washed with an organic solvent (preferably ether). The basic aqueous layer was acidified with an inorganic acid solution (e.g. aqueous HCl

solution). The aqueous (acidic) solution was then extracted several times into an organic solvent (e.g. ether or ethyl acetate). The combined organic layer was washed with brine, dried ($MgSO_4$ or Na_2SO_4) and concentrated to give the crude product 34 that may be used directly in the next step. However, purification may also be achieved by employing 5 known purification techniques (e.g. recrystallization) to provide pure compound 34; 1H -NMR ($CDCl_3$) δ 7.30 (d, 2H), 7.20 (s, 2H), 7.10 (d, 2H), 5.40 (s, 1H), 3.10 (s, 2H).

The method is an adaptation from a procedure previously described in US Patent No. 4,177,290 (issued on December 4, 1979) that is incorporated by reference herein in its entirety.

10 **Preparation of compound 35:**

Scheme 3, step 3: A solution of the thioacid 34 (9.0 g) in benzene was brought to reflux temperature and to it was slowly added 1.1 equivalents of thionyl chloride. The mixture was refluxed until the disappearance of the starting material (as evidenced by analytical techniques), cooled and the solvent removed to give the crude product 35 that 15 may be used directly in the next step. However, purification may also be achieved by employing known purification techniques (e.g. recrystallization) to provide pure compound 35.

Example 9: Synthesis of compound 36.

Scheme 3, step 4: The resulting thioacid chloride 35 (9.5 g) from the previous 20 step was taken into an appropriate organic solvent (preferably tetrahydrofuran or methylene chloride) and treated with ammonia gas (or 28% aqueous solution). The reaction mixture is then partitioned between water and ethyl acetate. The separated organic layer is washed with water, dilute acid, and brine, dried over a drying agent (e.g. $MgSO_4$ or Na_2SO_4) and concentrated to produce 6.40 g of compound 36. Analytical 25 Data: white solid; mp 88.5-89.5° C; R_t 9.61 min. 1H -NMR ($CDCl_3$) δ 7.40 (d, 2H), 7.30 (s, 2H), 7.20 (d, 2H), 6.40 (broad, 1H), 5.50 (broad, 1H), 5.40 (s, 1H), 3.10 (s, 2H).

Example 10: Synthesis of compound 37.

In a procedure similar to that of Example 9, treatment of 2.15 g of freshly prepared compound 35 with 2.2 g of n-propylamine generated a crude material that was

purified by flash column chromatography (eluent: 30% ethyl acetate in hexanes) to generate 1.71 g of compound 37. Analytical Data: viscous oil, R_t 12.30 min. $^1\text{H-NMR}$ (DMSO-d_6) δ 7.90 (t, 1H), 7.50 (d, 2H), 7.40 (s, 2H), 7.10 (d, 2H), 5.60 (s, 1H), 3.30 (d, 1H), 3.10 (m, 3H), 1.30 (m, 2H), 0.80 (t, 3H).

5 **Example 11:** Synthesis of compound 38.

In a procedure similar to that of Example 9, treatment of 2.56 g of freshly prepared compound 35 with dimethylamine gas generated a crude material that was purified by flash column chromatography (eluent: 30% ethyl acetate in hexanes) to produce 1.96 g of compound 38. Analytical Data: white solid; mp 71-72° C; R_t 11.08 min. $^1\text{H-NMR}$ (CDCl_3) δ 7.30-7.10 (m, 6H), 5.50 (s, 1H), 3.20 (s, 2H), 3.00 and 2.90 (2 sets of s, 6H).

Example 12: Synthesis of compound 39.

In a procedure similar to that of Example 9, treatment of 2.15 g of freshly prepared compound 35 with 2.74 g of diethylamine generated a crude product that was purified by flash column chromatography (eluent: 25% ethyl acetate in hexanes) to generate 1.56 g of compound 39. Analytical Data: white solid; mp 83-84° C; R_t 13.37 min. $^1\text{H-NMR}$ (CDCl_3) δ 7.30-7.10 (m, 6H), 5.60 (s, 1H), 3.40 (q, 2H), 3.30 (q, 2H), 3.20 (s, 2H), 1.10 (2 overlapping t, 6H).

Example 13: Synthesis of compound 40.

In a procedure similar to that of Example 9, treatment of 2.15 g of freshly prepared compound 35 with 4 g of morpholine generated a crude product that was purified by flash column chromatography (eluent: 50% ethyl acetate in hexanes) to generate 2.02 g of compound 40. Analytical Data: white solid; mp 75.5-78° C; R_t 11.21 min. $^1\text{H-NMR}$ (CDCl_3) δ 7.40-7.20 (2 sets of m, 6H), 5.50 (s, 1H), 3.70 (m, 4H), 3.60 (m, 2H), 3.40 (m, 2H), 3.20 (s, 2H).

Example 14: Synthesis of compound I-9.

To a cooled (-15° C to -25° C) solution of compound 36 (5.50 g) in either methylene chloride or chloroform, 1 equivalent of the oxidizing agent m-

chloroperoxybenzoic acid (m-CPBA) in the same solvent was slowly added. Stirring was continued at the low temperature until the disappearance of the starting material, as evidenced by various analytical techniques. The reaction mixture was then thoroughly washed with a saturated sodium bicarbonate solution, water and brine, respectively, dried over a drying agent (e.g. MgSO₄ or Na₂SO₄) and concentrated. The resulting material was then purified by column chromatography and/or recrystallization to give compound I-9 (5.50 g). Analytical Data: white solid, mp 131-132° C. ¹H-NMR (CDCl₃) δ 7.40 (m, 4H), 7.25 (d, 1H), 7.15 (d, 1H), 6.90 (broad, 1H), 5.60 (broad, 1H), 5.45 (s, 1H), 3.45 (d, 1H), 3.10 (d, 1H).

10 **Example 15:** Synthesis of compound I-10.

In a procedure similar to that of Example 14, compound 37 (1.67 g) was oxidized with 1 equivalent of the oxidizing agent m-chloroperoxybenzoic acid (m-CPBA), and then purified to give compound I-10 (1.40 g). Analytical Data: semi-solid; R_t 8.95 min. ¹H-NMR (DMSO-d₆) δ 8.00 (t, 1H), 7.40 (m, 4H), 7.10 (m, 2H), 5.30 (s, 1H), 3.20 (d, 1H), 3.10 (m, 1H), 3.00 (d, 1H), 2.90 (m, 1H), 1.20 (m, 2H), 0.80 (t, 3H).

15 **Example 16:** Synthesis of compound I-11.

In a procedure similar to that of Example 14, compound 38 (1.91 g) was oxidized with 1 equivalent of the oxidizing agent m-chloroperoxybenzoic acid (m-CPBA), and then purified to give compound I-11 (1.63 g). Analytical Data: white solid; mp 93-96° C; R_t 7.79 min. ¹H-NMR (CDCl₃) δ 7.50-7.30 (m, 6H), 5.70 (s, 1H), 3.60 (d, 1H), 3.40 (d, 1H), 3.10 and 2.90 (2 sets of s, 6H).

20 **Example 17:** Synthesis of compound I-12.

In a procedure similar to that of Example 14, compound 39 (1.53 g) was oxidized with 1 equivalent of the oxidizing agent m-chloroperoxybenzoic acid (m-CPBA), and then purified to give compound I-12 (1.35 g). Analytical Data: white solid; mp 93-95° C; R_t 9.70 min. ¹H-NMR (CDCl₃) δ 7.40-7.20 (m, 6H), 5.70 (s, 1H), 3.60 (d, 1H), 3.40 (m, 2H), 3.30 (d, 1H), 3.20 (m, 2H), 1.20 (t, 3H), 1.10 (t, 3H).

Example 18: Synthesis of compound I-13.

In a procedure similar to that of Example 14, compound **40** (2.00 g) was oxidized with 1 equivalent of the oxidizing agent m-chloroperoxybenzoic acid (m-CPBA), and then purified to give compound **I-13** (1.60 g). Analytical Data: white solid; mp 59-73°

5 C; R_f 8.03 min. $^1\text{H-NMR}$ (CDCl_3) δ 7.40-7.20 (2 sets of m, 6H), 5.60 (s, 1H), 3.80-3.20 (a series of m, 10H).

Example 19: Synthesis of compound I-22.

Compound **I-22** was prepared following the same multistep general method as described in Scheme A, utilizing 3-bromothiophene and benzaldehyde in step 1. (M + H)
10 = 280.

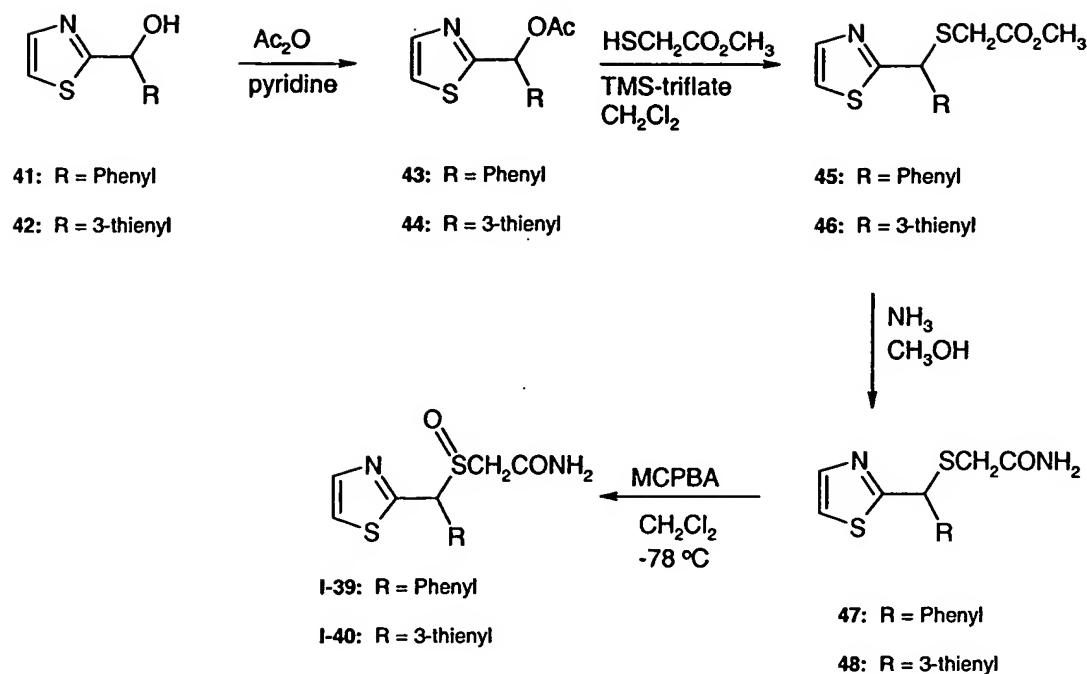
Examples 20-39: Synthesis of compounds I-1 through I-7 and I-26 through I-38.

Compounds **I-1** through **I-7** and **I-26** through **I-38** were prepared following the same multistep general method as described in Scheme A utilizing the appropriately substituted amine NHR_3R_4 in step 3b. The analytical data is represented by each
15 compound's mass spectrum (M + H) as shown in the following Table 3.

Table 3

Example	Compound	(M + H)
20	I-1	300
21	I-2	328
22	I-3	328
23	I-4	371
24	I-5	328
25	I-6	362
26	I-7	356
27	I-26	330
28	I-27	397
29	I-28	399
30	I-29	322
		(M + Na)
31	I-30	377
32	I-31	377
33	I-32	377
34	I-33	384
35	I-34	340
36	I-35	355
37	I-36	294
38	I-37	376
39	I-38	348

The following Examples 40-41 were synthesized according to Scheme 4.

Scheme 4

Preparation of Compound 43:

A mixture of compound 41 (0.75 g) (Dondoni, A. et. al. *J. Org. Chem.* 1988, pp. 1748-1761), acetic anhydride (3 equivalents) and anhydrous pyridine (2-3 mL/mmol of alcohol) was stirred overnight at room temperature, or until the reaction was complete by thin layer chromatography. The reaction mixture was then poured into cold water and extracted into ethyl acetate (3 x 25 mL). The combined organic phase was successively washed with saturated sodium bicarbonate solution, water, brine, dried (sodium sulfate) and concentrated to generate the desired product compound 43 (0.84 g). Analytical Data: $R_f = 0.6$ (2.5% methanol/ethyl acetate); $^1\text{H-NMR}$ (CDCl_3) δ 7.72 (s, 1H), 7.47 (m, 1H), 7.38-7.22 (m, 5H), 7.11 (s, 1H), 2.17 (s, 3H).

Preparation of Compound 44:

Compound 42 (0.92 g) was reacted in a manner similar to that described above in the preparation of compound 41. The resulting crude ester was purified by flash chromatography (eluent: 4:1 hexane/ethyl acetate) to give 0.41 g of compound 44.

Analytical Data: R_f = 0.32 (4:1 hexane/ethyl acetate); $^1\text{H-NMR}$ (CDCl_3) δ 7.83 (s, 1H), 7.42 (s, 1H), 7.36 (m, 1H), 7.17 (m, 1H), 7.00 (m, 1H), 2.19 (s, 3H).

Preparation of Compound 45:

To a stirring solution of compound 43 (0.84 g) and methyl thioglycolate (1.2 equivalents) in anhydrous dichloromethane (4-5 mL/mmol) at 0 °C under argon was added trimethylsilyl trifluoromethane (TMS-triflate, 1 equivalent). The reaction mixture was allowed to warm to room temperature and stirred until complete (2-6 h). It was then diluted with dichloromethane, washed with saturated sodium bicarbonate solution, dried (sodium sulfate), concentrated and dried under high vacuum to give compound 45 (1.01 g) that was used directly in the next step without any further purification. Analytical Data: R_f = 0.62 (2.5% methanol/ethyl acetate); $^1\text{H-NMR}$ (CDCl_3) δ 7.75 (s, 1H), 7.5 (d, 1H), 7.38-7.27 (m, 5H), 5.72 (s, 1H), 3.69 (s, 3H), 3.25 (q, 2H).

Preparation of Compound 46:

Compound 44 (0.41 g) was reacted in a manner similar to that described above in the preparation of compound 45 to give compound 46 (0.30 g). Analytical Data: R_f = 0.62 (2.5% methanol/ethyl acetate); $^1\text{H-NMR}$ (CDCl_3) δ 7.75 (s, 1H), 7.39 (s, 1H), 7.36 (m, 1H), 7.17 (broad, 1H), 6.94 (m, 1H), 6.07 (s, 1H), 3.72 (s, 3H), 3.30 (q, 2H).

Preparation of Compound 47:

Anhydrous ammonia was bubbled into a stirring solution of compound 45 (1.0 g) in methanol (10 mL/mmol) at 0 °C for 5-10 minutes. The reaction mixture was allowed to warm to room temperature, stirred for additional 5-7 h, concentrated under reduced pressure and dried under vacuum. The crude product was purified by flash chromatography (eluent: 5% methanol/ethyl acetate) to give 0.48 g of compound 47. Analytical Data: R_f = 0.20 (5% methanol/ethyl acetate); $^1\text{H-NMR}$ (CDCl_3) δ 7.77 (s, 1H), 7.47 (d, 1H), 7.44-7.27 (m, 5H), 5.53 (broad, 1H), 3.22 (q, 2H).

Preparation of Compound 48:

Compound 46 (0.30 g) was reacted in a manner similar to that described above in the preparation of compound 47 to give compound 48 (0.25 g). Analytical Data: R_f =

0.20 (5% methanol/ethyl acetate); $^1\text{H-NMR}$ (CDCl_3): δ 7.72, (s, 1H), 7.31 (s, 1H), 7.28 (m, 1H), 7.17 (s, 1H), 6.97 (m, 1H), 6.84 (broad, 1H), 6.11 (broad, 1H), 5.86 (s, 1H), 3.25 (q, 2H).

Example 40: Synthesis of compound I-39.

5 To a stirring solution of compound 47 (0.48) in anhydrous dichloromethane (10 mL/mmol) at -78°C was added a solution of *m*-CPBA (1.0 equivalent) in dichloromethane (5-8 mL/mmol). After an additional stirring for 1 h, the reaction mixture was allowed to warm to -30 to -40°C and quenched with 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution. Separated organic phase was successively washed with saturated sodium bicarbonate solution, water and brine, dried (sodium sulfate), and concentrated to generate compound I-37 (0.31 g). Analytical Data: R_f = 0.13 (5% methanol/ethyl acetate); $^1\text{H-NMR}$ (CDCl_3) major diastereomer: δ 7.92 (s, 1H), 7.61 (m, 2H), 7.44-7.36 (m, 5H), 7.00 (broad, 1H), 5.61 (s, 1H), 3.42 (q, 2H); minor diastereomer: δ 7.86 (s, 1H), 7.55 (m, 2H), 7.44-7.36 (m, 5H), 6.83 (broad, 1H), 5.55 (s, 1H), 3.61 (q, 2H).

10 15 **Example 41: Synthesis of compound I-40.**

Compound 48 (0.25 g) was reacted in a manner similar to that described above in the preparation of compound 47 to give compound I-39 (0.105 g) (diastereomeric mixture). Analytical Data: $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) major diastereomer: δ 8.03 (s, 1H), 7.92 (s, 1H), 7.78 (broad, 1H), 7.68 (s, 1H), 7.36 (broad, 1H), 7.17 (m, 1H), 6.50 (s, 1H), 3.47 (q, 2H); minor diastereomer: δ 7.97 (s, 1H), 7.86 (s, 1H), 7.78 (broad, 1H), 7.72 (s, 1H), 7.36 (broad, 1H), 7.22 (m, 1H), 6.39 (s, 1H), 3.36 (q, 2H).

Example 42: Synthesis of compound II-9.

Starting with 9-hydroxyfluorene, this compound was prepared following the same multistep general method as described in Scheme 3 above, and utilizing L-Alanine-
25 NH₂ in the amination step. Analytical Data: white solid (diastereomeric mixture); R_f 7.27 min and 7.41 min. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ 8.40-7.00 (a series of m and d, 11H), 5.60 and 5.70 (2 sets of s, 1H), 4.20 (m, 1H), 3.20 and 3.00 (2 sets of dd, 2H), 1.20 (2 overlapping doublets, 3H).

Example 43: Synthesis of compound II-23.

Starting with 9-hydroxyfluorene, this compound was prepared following the same multistep general method as described in Scheme 3 above, and utilizing 28% aqueous ammonia in the amination step. Analytical Data: white solid; mp 178.5-180° C; 5 R_t 7.48 min. 1H -NMR (CDCl₃) δ 7.90-7.40 (a series of m, 8H), 6.60 (broad, 1H), 5.40 (s, 1H), 5.30 (broad, 1H), 2.80 (d, 1H), 2.60 (d, 1H).

Example 44: Synthesis of compound II-25.

Starting with dibenzosuberol, this compound was prepared following the same multistep general method as described in Scheme 3 above, and utilizing 28% aqueous 10 ammonia in the amination step. Analytical Data: white solid; mp 182-190° C; R_t 8.43 min. 1H -NMR (DMSO-d₆) δ 7.80 (d, 1H), 7.60 (d, 1H), 7.40 (m, 8H), 5.50 (s, 1H), 3.60 (m, 2H), 3.50 (d, 1H), 3.40 (d, 1H), 2.90 (m, 2H).

Example 45: Synthesis of compound II-26.

Starting with dibenzosuberol, this compound was prepared following the same 15 multistep general method as described in Scheme 3 above, utilizing dimethylamine in the amination step. Analytical Data: white solid; mp 112.5-115° C; R_t 10.36 min. 1H -NMR (DMSO-d₆) δ 7.60 (d, 1H), 7.40 (m, 7H), 5.50 (s, 1H), 4.00 (d, 1H), 3.60 (d, 1H), 3.50 (m, 2H), 2.90 (s, 3H), 2.80 (m, 2H), 2.70 (s, 3H).

Examples 46-91: Synthesis of compounds II-6 through II-8, II-10 through II-15, II-24, 20 II-27, II-30 through II-54, II-56 through II-91.

Compounds II-6 through II-8, II-10 through II-15, II-24, II-27, II-30 through II-25 54, II-56 through II-91 were prepared following the same multistep general method as described in Scheme B incorporating the appropriate reactants to form the desired product. The analytical data is represented by each compound's mass spectrum (M + H) as shown in the following Table 4.

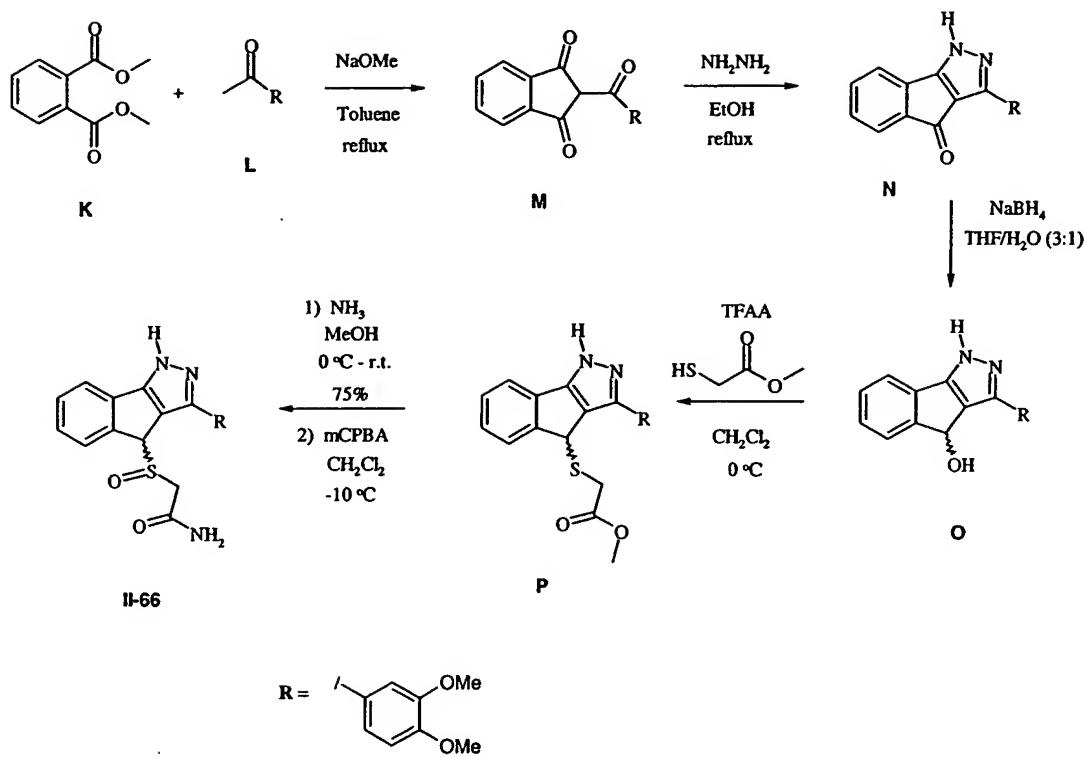
Table 4

Example	Compound	(M + H)
46	II-6	314
47	II-7	342
48	II-8	300
49	II-10	348
50	II-11	314
51	II-12	348
52	II-13	314
53	II-14	328
54	II-15	341
55	II-24	371
56	II-27	288
57	II-30	286
58	II-31	415
59	II-32	363
60	II-33	363
61	II-34	316
62	II-35	300
63	II-36	326
64	II-37	298
65	II-38	376
66	II-39	288
67	II-40	329
68	II-41	343
69	II-42	318
70	II-43	328
71	II-44	343
72	II-45	376

Example	Compound	(M + H)
73	II-46	330
74	II-47	358
75	II-48	343
76	II-49	343
77	II-50	371
78	II-51	359
79	II-52	373
80	II-53	369
81	II-54	286
82	II-56	316
83	II-57	359
84	II-58	314
85	II-59	328
86	II-60	334
87	II-61	340
88	II-62	385
89	II-63	384
90	II-64	338
91	II-65	384

The following Example 92 was synthesized according to Scheme 5.

Scheme 5



Preparation of Compound M:

A mixture of dimethyl phthalate (compound K, 10 g, 0.51 mol), 3,4-dimethoxyacetophenone (compound L, 9.74 g, 0.054 mol), and powdered sodium methoxide (2.76 g, 0.051 mol) was heated at reflux overnight, cooled to room temperature, and concentrated *in vacuo*. The yellow slurry was suspended in water (100 mL), stirred for 10 min, acidified with 6N HCl (pH ~ 1-2), and filtered. The residue was placed in ethanol (200 mL), heated to reflux for 30 min, cooled to room temperature, and filtered. The residue was washed with cold ethanol and dried *in vacuo* to generate compound M as a bright yellow fluffy solid (4.1 g) that was used without any further purification. Analytical Data: $^1\text{H-NMR}$ (CDCl_3) δ 3.99 (s, 3H), 4.02 (s, 3H), 6.99 (d, 1H), 7.68-7.75 (m, 2H), 7.85 (m, 2H), 8.07 (d, 1H), 8.09 (s, 1H); MS: $(\text{M}+\text{H})^+ = 311$.

Preparation of Compound N:

A mixture of compound M (3.37 g, 0.011 mol), hydrazine (0.41 mL, 0.013 mol) and ethanol (250 mL) under nitrogen was heated to reflux for 6 h, cooled to room temperature and filtered. The residue was washed with ethanol and dried to give 5 compound N as a yellow solid (2.0 g). Analytical Data: ^1H NMR (CDCl_3) δ 3.85 (s, 3H), 3.89 (s, 3H), 7.17 (d, 1H), 7.38-7.43 (m, 1H), 7.55 (m, 2H), 7.60 (d, 1H), 7.85 (d, 1H), 7.95 (s, 1H); MS: $(\text{M}+\text{H})^+ = 307$.

Preparation of Compound O:

To a stirred solution of compound N (0.084 g, 0.27 mmol) in $\text{THF}/\text{H}_2\text{O}$ (3:1, 8 mL) at room temperature under nitrogen was added solid sodium borohydride (0.029 g, 0.63 mmol) in one portion. The reaction mixture was cooled to 0 °C, stirred for 1 h, warmed to room temperature, diluted with ethyl acetate and washed with water. The 10 organic phase was dried (magnesium sulfate) and concentrated *in vacuo*. The residue, on trituration with ether, generated compound O (0.077 g) as a yellow solid that was used 15 without further purification. Analytical Data: ^1H NMR (CDCl_3) δ 3.86 (s, 3H), 3.87 (s, 3H), 5.53 (s, 1H), 6.79 (d, 1H), 7.29 (t, 2H), 7.46 (d, 1H), 7.50 (s, 2H), 7.58 (t, 1H); MS: $(\text{M}+\text{H})^+ = 309$.

Preparation of Compound P:

To a stirred solution of compound O (1.55 g, 0.005 mol) in CH_2Cl_2 (40 mL) 20 under nitrogen at 0 °C was added methyl thioglycolate (0.54 mL, 0.006 mmol). Next, trifluoroacetic anhydride (1.42 mL, 0.01 mol) was added dropwise to the reaction mixture. The reaction mixture was stirred at 0 °C for 0.5 h, warmed to room temperature, stirred overnight, quenched with saturated aqueous sodium bicarbonate and extracted into ethyl acetate (3 x 25 mL). The organic layer was washed with water, 25 brine, dried (magnesium sulfate), and concentrated *in vacuo* to generate compound P as a yellow solid (1.75 g) that was used without any further purification. Analytical Data: ^1H NMR (CDCl_3) δ 2.77 (q, 2H), 3.33 (s, 3H), 3.93 (s, 3H), 4.00 (3H), 4.99 (s, 1H), 6.96 (d, 1H), 7.23-7.42 (m, 2H), 7.47 (d, 1H), 7.49 (d, 1H), 7.64 (d, 1H), 7.69 (d, 1H), 7.72 (d, 1H); MS: $(\text{M}+\text{H})^+ = 397$.

Example 92: Synthesis of compound II-66.

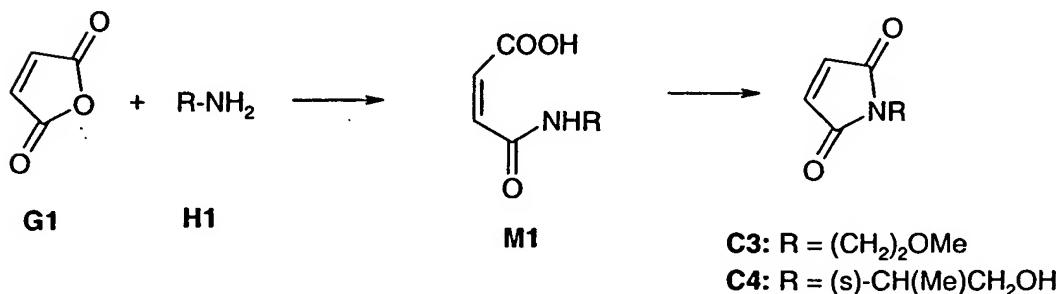
Starting from compound **P**, this compound was generated following the procedure as described above for the preparation of compound **47**, and in Example 35 for the synthesis of compound **I-37**. Thus, 0.050 mg of compound **P**, on treatment with 5 ammonia in the first step, followed by oxidation with *m*-CPBA in the next step, generated 0.011 g of compound **II-66**. Analytical Data: $^1\text{H-NMR}$ (CDCl_3) δ 2.75 (d, 1H), 2.88 (d, 1H), 3.92 (s, 3H), 3.96 (s, 3H), 5.67 (s, 1H), 6.80 (s, 1H), 6.94 (d, 1H), 7.37 (t, 1H), 7.45-7.52 (m, 2H), 7.58 (d, 1H), 7.64 (s, 1H), 7.79 (d, 1H); MS: $(\text{M}+\text{H})^+ = 420$.

Compounds of formula (VI) and (VIII) (Tables 2A and 2B) are readily prepared 10 using the appropriate cyclic maleimides. For example, the cyclic maleimides used in the preparation compounds **VI-1, 2, 6, 7, 8** (Table 2A) and **VIII-1, 2, 6, 8** (Table 2B) are commercially available. Other cyclic maleimides are known in the literature (see, for example, Bayer et al. *Montash. Chem.* 1997, 91 and Kakiuchi et al. *Chem. Lett.* 1998, 1001, both of which are incorporated by reference herein in their entirety).

15 In addition, a general synthetic scheme is set forth in Scheme 6 for preparation of cyclic imides (**C3** and **C4**) utilized in the synthesis of compounds **VI-3, 5** (Table 2A) and **VIII-3, 4** (Table 2B).

Scheme 6

20



25 In Scheme 6, the reaction of maleic anhydride (compound **G1**) with an appropriate amine (compound **H1**, wherein R is $-(\text{CH}_2)_2\text{OMe}$ or $(\text{s})\text{-CH}(\text{Me})\text{CH}_2\text{OH}$) generates the corresponding maleimic acid (compound **M1**). Cyclization of compound

M1 in presence of $\text{Ac}_2\text{O}/\text{NaOAc}$ at room temperature or in toluene/triethylamine under reflux conditions generates compounds **C3** and **C4**.

Preparation of Compound C3:

5 To a solution of maleic anhydride (compound **G1**, 1 equiv.) in acetic acid was added 2-methoxyethylamine (compound **H1**, $\text{R} = (\text{CH}_2)_2\text{OMe}$, 1 equiv.) in a dropwise fashion. After stirring overnight at room temperature, the reaction mixture was concentrated to generate crude compound **M1** that was taken in a mixture of acetic anhydride and NaOAc (0.6 equiv.). The resulting mixture was stirred at 90°C for 2h, 10 cooled to room temperature, quenched with cold water and extracted into ether. The combined organic layers were washed with brine, dried (magnesium sulfate) and concentrated to generate compound **C3**, which was directly used without further purification; $^1\text{H-NMR}$ (DMSO-d_6): δ 7.02 (s, 2H), 3.54 (m, 2H), 3.44 (m, 2H), 3.20 (s, 3H).

15

Preparation of Compound C4:

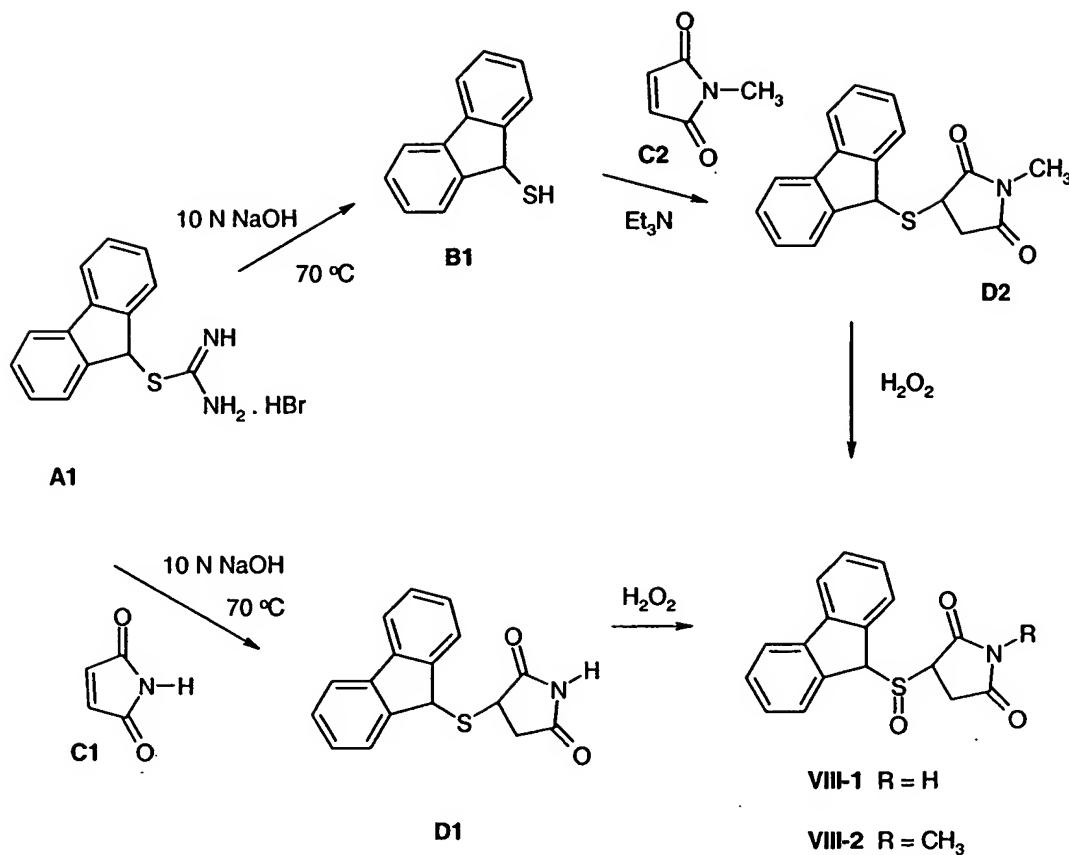
A solution of (*S*)-2-aminopropanol (compound **H1**, $\text{R} = (\text{s})\text{-CH}(\text{Me})\text{CH}_2\text{OH}$, 1 equiv.) in absolute ethanol was slowly added to a solution of maleic anhydride (compound **G1**, 1 equiv.). The resulting mixture was stirred at room temperature 20 overnight. The separated solid was filtered, washed with ether, taken into toluene and treated with triethylamine. The resulting mixture was refluxed for 4 h under a Dean-Stark trap, cooled to room temperature, concentrated and passed through a pad of silica gel (eluent: ethyl acetate) to give compound **C4**; $^1\text{H-NMR}$ (Acetone-d_6): δ 6.80 (s, 2H), 4.20 (m, 1H), 3.91 (m, 2H), 3.64 (m, 1H), 1.29 (d, 3H).

25

The following Examples **92a-92q** were synthesized following the procedures outlined in Scheme 7.

30

Scheme 7



5

In Scheme 7, the reaction of an appropriate thiol (generated from corresponding thiouronium salt), with an appropriate cyclic imide in presence of a base generates the corresponding thioether. The thioether may be oxidized to give the corresponding sulfoxide. For example, thiol B1, generated from its corresponding thiouronium salt A1 (prepared from compound A as disclosed in Scheme 1), reacts with N-methylmaleimide (compound C2) in presence of triethylamine to generate thioether D2 that on subsequent oxidation with hydrogen peroxide in glacial acetic acid produces the corresponding sulfoxide, compound VIII-2 (Table 2B). Alternatively, the thioether may be directly produced by reacting the appropriate thiouronium salt with the appropriate cyclic imide in the presence of a base. Thus, thioether D1 was directly produced from the reaction of

its corresponding thiouranium salt **A1** with maleimide (**C1**), in presence of 10 N NaOH. Oxidation of **D1** generated the corresponding sulfoxide **VIII-1** (Table 2B).

Example 92a: Synthesis of compound **VIII-1**.

5 A mixture of compound **A1** (4 g, 12.46 mmol.), 10 N NaOH (4 mL) and water (10 mL) was stirred at 70 °C for 0.5 h. Maleimide (compound **C1**, 1.2 g, 12.37 mmol.) in ethanol (20 mL) was then added to the reaction mixture and stirring was continued at 70 °C for another 2 h. After cooling to room temperature, the separated solid was filtered, washed successively with water, hexane and ether. The filtrate containing the 10 desired product was extracted into ethyl acetate. The combined organic layers were washed successively with water and brine, dried (MgSO_4), and concentrated to furnish the crude product that was purified by flash chromatography (hexane:ethyl acetate 1:1) to give 0.510 g of compound **D1**; $^1\text{H-NMR}$ (DMSO-d_6): δ 11.33 (s, 1H), 7.90-7.32 (a series of m, 8H), 5.49 (s, 1H), 3.79 (dd, 1H), 2.64 (dd, 1H), 2.24 (dd, 1H).

15 Oxidation of compound **D1** with hydrogen peroxide, as described above, generated the title compound as a mixture of diastereomers; R_t = 10.16 min; $^1\text{H-NMR}$ (DMSO-d_6): δ 11.82 (s, 0.11 H), 11.44 (s, 0.89 H), 8.03-7.39 (a series of m, 8 H), 5.99 (s, 0.11 H), 5.72 (s, 0.89 H), 4.58 (m, 0.11 H), 3.22 (dd, 0.89 H), 2.79 (dd, 3.32, 0.11H), 20 2.55 (dd, 0.89H), 1.67 (dd, 0.89H). MS: 312 (M + H), 334 (M + Na).

Example 92b: Synthesis of compound **VIII-2**.

25 A mixture of compound **A1** (1 equiv) in water and 10 N NaOH (4-5 equiv) was stirred at 70°C for 3-5 h. The mixture was cooled to 0°C, acidified with dil HCl and extracted into ether. The combined organic layers were washed with brine, dried (magnesium sulfate), and concentrated to furnish compound **B1** that was used without further purification; $^1\text{H-NMR}$ (DMSO-d_6): δ 7.87-7.35 (a series of m, 8H), 5.21 (d, 1H), 3.55 (d, 1H).

30 A mixture of compound **B1** (1 equiv.), compound **C2** (1 equiv.), and triethylamine in ethyl acetate:methanol (4:1) was stirred at room temperature for 2-5 h, concentrated and purified by flash chromatography (hexane:ethyl acetate 2:1) to give

compound D2; $^1\text{H-NMR}$ (DMSO- d_6): δ 7.90-7.35 (series of m, 8H), 5.49 (s, 1H), 3.76 (m, 1H), 2.73 (s, 3H), 2.61(dd, 1H), 2.24 (dd, 1H).

Oxidation of compound **D2** with hydrogen peroxide, as described above,
 5 generated the title compound as a mixture of diastereomers; R_f 10.30 min; $^1\text{H-NMR}$ (DMSO-d₆): δ 8.04-7.37 (a series of m, 8H), 5.98 (s, 0.08H), 5.77 (s, 0.92H), 4.61 (m, 0.08H), 3.31-2.50 (a series of m and dd, 5.08H), 1.58 (dd, 0.92H). MS: 348 (M + Na).

Example 92c: Synthesis of compound VI-1.

10 The title compound was prepared using the appropriate starting materials and following the methodologies described above. Analytical data: R_f 9.20 min. and 9.41 min (diastereomers); ¹H-NMR (DMSO-d₆): δ 11.62 and 11.53 (2 singlets, 1H), 7.57-7.32 (a series of m, 10H), 6.07 (s, 0.4H), 5.33 (s, 0.6H), 3.74 (m, 0.6H), 3.55 (m, 0.4H), 3.14 (dd, 0.4H), 2.96 (dd, 0.6H), 2.82 (dd, 0.4H), 2.57 (dd, 0.6H). MS: 312 (M-H).

15

Example 92d: Synthesis of compound VI-2.

The title compound was prepared using the appropriate starting materials and following the methodologies described above. Analytical data: R, 8.05 min. and 8.17 min (diastereomers). $^1\text{H-NMR}$ (DMSO- d_6): δ 7.58-7.26 (a series of m, 10H), 6.04 (s, 1H), 3.31-2.49 (a series of m, 6H). MS: 350 (M + Na).

Example 92e: Synthesis of compound VI-3.

The title compound was prepared using the appropriate starting materials and following the methodologies described above. Analytical data: R_f 8.38 min and 8.46 min (diastereomers); ¹H-NMR (DMSO-d₆): δ 7.58-7.01 (a series of m, 10H), 6.03 (s, 0.23H), 5.38 (s, 0.77H), 3.84-3.01 (a series of m, 9.23H), 2.61 (dd, 0.77H). MS: 394 (M + Na).

Example 92f: Synthesis of compound VI-4.

30 The title compound was prepared using the appropriate starting materials and following the methodologies described above. Analytical data: R, 7.38 min. (overlapping diastereomers); $^1\text{H-NMR}$ (DMSO- d_6): δ 7.58-7.33 (a series of m, 10H),

6.02 (s, 0.33H), 5.38 (s, 0.67H), 4.67 (m, 1H), 3.79-2.94 (a series of m, 5.33H), 2.60 (dd, 0.67H). MS: 380 (M + Na).

Example 92g: Synthesis of compound VI-5.

5 The title compound was prepared using the appropriate starting materials and following the methodologies described above. Analytical data: R, 7.98 min, 8.16 min, and 10.42 min (diastereomers); $^1\text{H-NMR}$ (DMSO-d₆): δ 7.58-7.35 (a series of m, 8H), 6.03 and 6.02 (two overlapping s, 0.46H), 5.36 (s, 0.54H), 4.70 (m, 0.54H), 4.14-2.50 (series of m, 6H), 1.22-1.12 (overlapping d, 3H). MS: 372(M + H), 394 (M + Na).

10

Example 92h: Synthesis of compound VI-6.

The title compound was prepared using the appropriate starting materials and following the methodologies described above. Analytical data: R, 7.78 min and 7.88 min (diastereomers); $^1\text{H-NMR}$ (DMSO-d₆): δ 7.63-7.22 (two m, 8H), 6.06 (s, 0.66H), 15 5.47 (s, 0.34H), 3.82 (m, 0.34H), 3.69(m, 0.66H), 3.14(dd, 0.66H), 2.95(m, 1H), 2.84 and 2.81 (two s, 3H), 2.9 (dd, 0.34H). MS: 386 (M+Na).

Example 92i: Synthesis of compound VI-7.

20 The title compound was prepared using the appropriate starting materials and following the methodologies described above. Analytical data: R, 8.48 min and 8.70 min (diastereomers); $^1\text{H-NMR}$ (DMSO-d₆): δ 11.52 (br, 1H), 7.69-7.60 (m, 4H), 7.29 (m, 2H), 6.32 (s, 0.1H), 5.60 (s, 0.9H), 3.75 (m, 1H), 3.81 (dd, 1H), 2.66-2.32 (m, 1H). MS: 348 (M + Na).

25 **Example 92j: Synthesis of compound VI-8.**

The title compound was prepared using the appropriate starting materials and following the methodologies described above. Analytical data: R, 8.70 min (overlapping diastereomers). $^1\text{H-NMR}$ (DMSO-d₆): δ 11.62 and 11.53 (two br, 1H), 7.74-7.25 (m, 8H), 6.18 and 6.13 (two s, 0.4H), 5.47 and 5.45 (two singlets, 0.6H), 3.78-2.49 (a series 30 of m, 3H). MS: 342 (M + Na).

Example 92k: Synthesis of compound VIII-3.

The title compound was prepared using the appropriate starting materials and following the methodologies described above. Analytical data: R_t 10.79 min. and 10.98 min (diastereomers). $^1\text{H-NMR}$ (DMSO- d_6): δ 8.04-7.37 (a series of m, 8H), 5.97 (s, 0.5H), 5.75 (s, 0.5H), 4.65 (m, 0.5H), 3.69-2.55 (a series of m, 2.08H), 1.65 (dd, 0.5H).
5 MS: 392 (M + Na).

Example 92l: Synthesis of compound VIII-4.

The title compound was prepared using the appropriate starting materials and
10 following the methodologies described above. Analytical data: R_t 9.18 min and 9.30 min (diastereomers); $^1\text{H-NMR}$ (DMSO- d_6): δ 8.05-7.37 (a series of m, 8H), 5.96 (s, 0.09H), 5.77 (s, 0.91H), 4.80 and 4.48 (two m, 1H), 3.57-2.49 (a series of m, 5.09H), 1.51 (dd, 0.91H). MS: 378 (M + H), 403 (M + Na).

15 **Example 92m: Synthesis of compound VIII-5.**

The title compound was prepared using the appropriate starting materials and following the methodologies described above. Analytical data: R_t 10.03 min, 10.30 min, 10.42 min and 11.11 min (diastereomers). $^1\text{H-NMR}$ (DMSO- d_6): δ 8.05-7.37 (a series of m, 8H), 5.95 and 5.94 (two overlapping singlets, 0.36H), 5.76 (s, 0.64H), 4.85-2.49 (a series of m, 6H), 1.29 and 1.08 (two sets of overlapping d, 3H). MS: 370 (M + H), 392 (M + Na).

Example 92n: Synthesis of compound VIII-6.

The title compound was prepared using the appropriate starting materials and
25 following the methodologies described above. Analytical data: R_t 7.22 min (overlapping diastereomers); $^1\text{H-NMR}$ (DMSO- d_6): δ 11.23 and 10.89 (two singlets, 1H), 8.04-7.38 (a series of m, 8H), 6.00 (s, 0.37H), 5.77 (s, 0.63H), 4.65 (m, 0.37H), 3.32 (m, 0.63H), 3.22 (dd, 0.37H), 2.86 (dd, 0.37H), 2.59 (dd, 0.63H), 1.76 (dd, 0.63H). MS: 328 (M + H), 350 (M + Na).

Example 92o: Synthesis of compound VIII-7.

The title compound was prepared using the appropriate starting materials and following the methodologies described above. Analytical data: R, 13.90 min and 14.12 min (diastereomers); $^1\text{H-NMR}$ (DMSO- d_6): δ 8.04-6.80 (a series of m, 12H), 5.98 (s, 0.11H), 5.76 (s, 0.89H), 4.65 (d, 0.22H), 4.37 (s, 1.78H), 3.69 (s, 3H), 3.31 (m, 1H), 2.93 (m, 0.11H), 2.63 (dd, 0.89H), 1.78 (dd, 1H). MS: 554 (M + Na).

Example 92p: Synthesis of compound VIII-8.

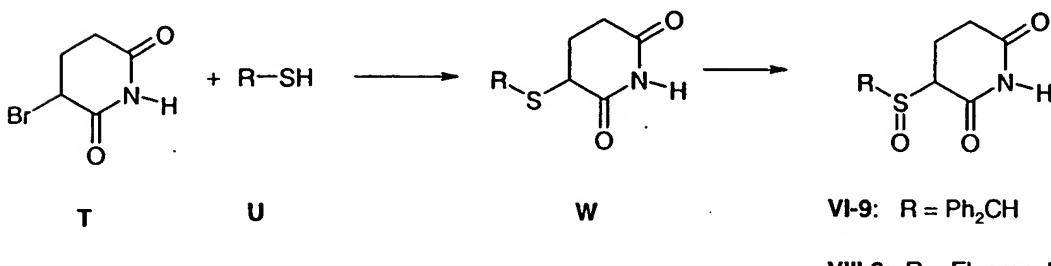
The title compound was prepared using the appropriate starting materials and following the methodologies described above. Analytical data: R, 9.48 min and 9.62 min (diastereomers); $^1\text{H-NMR}$ (DMSO- d_6): δ 8.04-7.09 (a series of m, 13H), 5.97 (s, 0.1H), 5.84 (s, 0.9H), 4.70 (m, 0.1H), 3.38-3.24 (m, 1H), 3.04 (m, 0.1H), 2.72 (dd, 0.9H), 1.63 (dd, 0.9H). MS: 388 (M + H), 410 (M + Na).

15 Example 92q: Synthesis of compound VII-1.

The title compound was prepared from compound A1 (Scheme 7) following the similar procedure as described for the synthesis of compound VIII-1 with the exception of utilizing 3-bromo-1-phenyl-pyrrolidin-2-one in place of maleimide in the first step. Analytical data: R, 9.36 min and 9.72 min (mixture of diastereomers); $^1\text{H-NMR}$ (DMSO- d_6): δ 8.03-7.12 (a series of m, 13H), 6.19 (s, 0.1H), 5.66 (s, 0.9H), 3.71-3.28 (three m, 3H), 2.32 (m, 1H), 1.30 (m, 1H). MS: 374 (M + H), 396 (M + Na).

25 The following Examples 92r-92s were synthesized according to Scheme 8.

Scheme 8



In Scheme 8, the reaction of an appropriate thiol (compound U) with 3-bromo-glutarimide (T), in presence of a base, generated corresponding compound W. Oxidation of appropriate compound W produced compounds VI-9 and VIII-9, 5 respectively. 3-Bromoglutarimide was prepared from procedures described in Japanese Patent Application No. 8308, 1961 and Japanese Patent Application No. 5277, 1960, both of which are incorporated by reference herein in their entirety.

Example 92r: Synthesis of compound VI-9.

10 To a cooled (0°C) solution of diphenylmethylthiol (1 equiv.) and 3-bromo-glutarimide (1 equiv.) in dry tetrahydrofuran, DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene)(1.05 equiv.) was added dropwise. The cooling bath was removed and the mixture was stirred at room temperature for 1-2 h, diluted with hexane:ethyl acetate (1:1) and washed successively with water and brine. Drying (magnesium sulfate) and solvent 15 evaporation gave a crude product that was triturated with ethyl acetate to generate intermediate compound W (where R = Ph₂CH); ¹H-NMR (DMSO-d₆): δ 10.81(s, 1H), 7.53-7.22 (a series of m, 10H), 5.52 (s, 1H), 3.3-1.81 (a series of m, 5H).

20 Oxidation of above-prepared compound W with hydrogen peroxide, following previously disclosed methodology, generated the title compound as a mixture of diastereomers; R_t 9.20 min and 9.44 min; ¹H-NMR (DMSO-d₆): δ 11.17 & 11.12 (two singlets, 1H), 7.57-7.33 (a series of m, 10H), 5.75 (s, 0.35H), 5.43 (s, 0.65H), 3.45-2.53 (a series of m, 5H). MS: 350 (M + Na).

25 **Example 92s: Synthesis of compound VIII-9.**

Following the same procedures as described above for the synthesis of VI-9, the title compound, starting from 9-fluorenylthiol, was also prepared as a diastereomeric mixture; R_t 7.18 min and 7.47 min; ¹H-NMR (DMSO-d₆): 11.32 and 11.16 (two singlets, 1H), 7.99-7.35 (a series of m, 8H), 5.79 and 5.66 (two singlets, 1H), 4.26 and 4.07 (two 30 multiplets, 1H), 2.70-2.10 (a series of m, 4H). MS: 326 (M + H), 348 (M + Na).

Example 93: Demonstration of Wake-promoting activity of compound I-9.

The methodology utilized is as described by Edgar and Seidel, Journal of Pharmacology and Experimental Therapeutics, 283:757-769, 1997, incorporated herein in its entirety by reference.

5 **Animal Surgery.** Adult, male Wistar rats (275-320g from Charles River Laboratories, Wilmington, MA) were anesthetized (Nembutal, 60mg/kg, ip) and surgically prepared with implants for recording of chronic EEG and EMG recording. The EEG implants consisted of stainless steel screws (2 frontal (+3.9 AP from bregma, $\pm 2.0\text{ML}$) and 3 occipital (-6.4 AP, $\pm 5.5\text{ML}$). Two Teflon-coated stainless steel wires 10 were positioned under the nuchal trapezoid muscles for EMG recording. All leads were soldered to a miniature connector (Microtech, Boothwyn, PA) and gas sterilized with ethylene oxide before surgery. The implant assembly was affixed to the skull by the combined adhesion of the EEG recording screws, cyanoacrylate applied between the hermetically sealed implant connector and skull and dental acrylic. An antibiotic 15 (Gentamycin) was administered for 3 to 5 days postsurgery. At least 3 weeks were allowed for postsurgical recovery.

20 **Recording environment.** Rats were housed individually within specially modified Nalgene microisolator cages equipped with a low-torque slip-ring commutator (Biella Engineering, Irvine, CA) and a custom polycarbonate filter-top riser. These cages were isolated in separate, ventilated compartments of a stainless steel sleep-wake recording chamber. Food and water were available *ad libitum* and ambient temperature was $24 \pm 1^\circ\text{C}$. A 24-h light-dark cycle (light/dark 12-12-) was maintained throughout the study by 4-watt fluorescent bulbs located approximately 5cm from the top of each cage. Light intensity was 30 to 35 lux at midlevel inside the cage. Animals were 25 undisturbed for 3 days both before and after the treatments.

25 **Automated data collection.** Sleep and wake stages were determined with SCORE, a microcomputer-based sleep-wake and physiological monitoring system. SCORE™ design features, validation in rodents and utility in preclinical drug evaluation have been reported elsewhere (Van Gelder, *et al.*, 1991; Edgar, *et al.*, 1991, 1997; Seidel, 30 *et al.*, 1995, incorporated by reference herein in their entirety). In the present study, the system monitored amplified (X 10,000) EEG (bandpass, 1-30 Hz; digitization rate, 100 Hz) and integrated EMG (bandpass, 10-100 Hz, root mean square integration). Arousal

states were classified on-line as NREM sleep, REM sleep, wake or theta-dominated wake every 10s by use of EEG period and amplitude feature extraction and ranked membership, algorithms. Individually taught EEG-arousal-state templates and EMG criteria differentiated REM sleep from theta-dominated wakefulness (Welsh, *et al.*, 1985,

5 incorporated by reference herein in its entirety). Data quality was assured by frequent on-line inspection of the EEG and EMG signals. Raw data quality and sleep-wake scoring was scrutinized further by a combination of graphical and statistical assessments of the data as well as visual examination of the raw EEG wave forms and distribution of integrated EMG values.

10 **Drug administration and study design.** Compound I-9 was suspended in sterile 0.25% methylcellulose (pH=6.2; Upjohn Co., Kalamazoo, MI) or methylcellulose vehicle alone was injected intraperitoneally in a volume of 1ml/kg. Sample size (*n*) was 13 animals per treatment group.

15 **EEG spectral analysis.** Each 10-s epoch of raw EEG signal was digitized (100 Hz) for 24h and wakefulness was scored as described previously by Edgar and Seidel (1996), incorporated by reference herein in its entirety.

20 **Data analysis and statistics.** The principal variable recorded was minutes per hour of wake. Treatment groups were compared post-treatment by repeated-measures ANOVA. In the presence of a significant main effect, Dunnett's contracts ($\alpha = 0.05$) assessed differences between active treatment groups and vehicle controls, unless otherwise specified.

25 **Results.** Figure 1 illustrates degree of wakefulness in rats treated at time zero with either 100 mg/kg, ip of compound I-9 (solid line) or methylcellulose vehicle (stippled line). Compound I-9 produced wakefulness beyond that observed in vehicle-treated animals that lasted until approximately 110 minutes following administration.

Example 94: Demonstration of Wake-promoting activity of compound II-23.

The methodology utilized is based on that described by Edgar and Seidel, Journal of Pharmacology and Experimental Therapeutics, 283:757-769, 1997, and incorporated herein in its entirety by reference.

30 **Animal Surgery.** Adult, male Wistar rats (275-320g from Charles River Laboratories, Wilmington, MA) were anesthetized (Nembutal, 45mg/kg, ip) and surgically

prepared with implants for recording of chronic EEG and EMG recording. The EEG implants were made from commercially available components (Plastics One, Roanoke, VA). EEG's were recorded from stainless steel screw electrodes (2 frontal (+3.0 mm AP from bregma, ± 2.0 mm ML) and 2 occipital (-4.0 mm AP, ± 2.0 mm ML)). Two Teflon-coated 5 stainless steel wires were positioned under the nuchal trapezoid muscles for EMG recording. All electrode leads were inserted into a connector pedestal and the pedestal, screws, and wires affixed to the skull by application dental acrylic. Antibiotic was administered post surgically and antibiotic cream was applied to the wound edges to prevent infection. At least 1 week elapsed between surgery and recording. Animals are tested for approximately 10 6-8 weeks and then sacrificed.

Recording environment. Postsurgically, rats were housed individually in an isolated room. At least 24 hrs. prior to recording, they were placed in Nalgene containers (31 x 31 x 31 cm) with a wire-mesh top, and entry to the room was prohibited until after recording had ended except for dosing. The containers were placed on a 2- 15 shelf rack, 4 per shelf. Food and water were available *ad libitum*, ambient temperature was 21°C, and humidity was 55%. White-noise was provided in the background (68db inside the containers) to mask ambient sounds. Fluorescent overhead room lights were set to a 24 hr. light/dark cycle (on at 7 AM, off at 7 PM). Light levels inside the containers were 38 and 25 lux for the top and bottom shelves respectively.

20 **Data acquisition.** EEG and EMG signals were led via cables to a commutator (Plastics One) and then to pre-amplifiers (model 1700, A-M Systems, Carlsborg, WA). EEG and EMG signals were amplified (10K and 1K respectively) and bandpass filtered between 0.3 and 500 Hz for EEG, and between 10 and 500 Hz for EMG. These signals were digitized at 128 samples per second using ICELUS sleep research software (M. 25 Opp, U. Texas; see Opp, Physiology and Behavior 63:67-74, 1998, and Imeri, Mancia, and Opp, Neuroscience 92:745-749, 1999, incorporated by reference herein in their entirety) running under Labview 5.1 software and data acquisition hardware (PCI-MIO-16E-4; National Instruments, Austin, TX). On the day of dosing, data was recorded from 11 AM to 6 PM.

30 **Sleep / wake scoring.** Sleep and wake stages were determined manually using ICELUS software. This program displays the EEG and EMG data in blocks of 6 sec. along with the EEG-FFT. Arousal state was scored as awake (WAK), rapid eye-

movement (REM), or slow-wave or non-REM sleep (NREM) according to visual analysis of EEG frequency and amplitude characteristics and EMG activity (Opp and Krueger, American Journal of Physiology 266:R688-95, 1994; Van Gelder, *et al.*, 1991; Edgar, *et al.*, 1991, 1997; Seidel, *et al.*, 1995, incorporated by reference herein in their entirety). Essentially, waking activity consists of relative low-amplitude EEG activity with relatively lower power in the lower frequency bands from 0.5 – 6 Hz, accompanied by moderate to high level EMG activity. In a particular waking state (“theta-waking”), EEG power can be relatively focused in the 6-9 Hz (theta) range, but significant EMG activity is always present. NREM sleep is characterized by relative high-amplitude EEG activity with relatively greater power in the low frequency bands from 0.5 - 6 Hz, accompanied by little or no EMG activity. REM sleep is characterized by moderate and constant amplitude EEG focused in the theta (6-9 Hz range), similar to waking theta, but with no EMG activity.

Drug administration and study design. Compounds were evaluated on groups of 4 or 8 rats which were tested in 2 sessions at least 2 days apart. Initial studies used a crossover design, such that rats received either vehicle or test compound during each session. Animals were pseudo-randomized so that they did not receive the same drug twice. Compound II-23 was suspended in sterile 0.25% methylcellulose (pH=6.2; Upjohn Co., Kalamazoo, MI) at 30 mg/ml. This study was carried out on 8 rats which were tested in 2 sessions 5 days apart (overall, 7 rats received compound II-23 and 6 methylcellulose vehicle). Dosing was carried out at noon, while the rats were predominantly asleep. Each rat was lifted out of its container, given an intraperitoneal injection in a volume of 3.33 ml/kg, and replaced. Dosing required approximately 8 minutes.

Data analysis and statistics. The principal outcome measure was minutes per hour of wakefulness. The primary outcome measure for purposes of determining activity in these experiments consists of the total integrated wake time for the first 3 hours post dosing relative to vehicle control. Thus, vehicle treated animals typically average 20% wake time during the recording period, or a total of $0.2 * 180 = 36$ min. A 2-tailed, unpaired t-test (Statview 5.0, SAS Institute, Inc., Cary, NC) was performed on the wake time values for drug and vehicle treated animals, and compounds with $p < 0.05$ were deemed significantly wake-promoting. Waking activity was also evaluated for

successive half-hour periods beginning with the time of dosing, and individual t-tests performed at each time point to establish the duration of significant wake-promoting activity.

5 **Results.** Figure 2 illustrates degree of wakefulness in rats treated at noon with either 100 mg/kg, ip. of compound II-23 (solid triangles) or methylcellulose vehicle (open circles). Each point represents the mean percent of time awake for the succeeding half hour. The dosing procedure produced a transient (~20 min.) period of elevated wakefulness in both treatment groups compared to pre-dosing baseline activity. Compound II-23 produced significantly greater wakefulness than that observed in 10 vehicle-treated animals (p<0.05).

15 **References.** The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated in their entirety herein by reference:

Touret, *et al.*, *Neuroscience Letters*, **189**:43-46, 1995.
15 Van Gelder, R.N. *et al.*, *Sleep* **14**:48-55, 1991.
Edgar, D.M., *J. Pharmacol. Exp. Ther.* **282**:420-429, 1997.
Edgar and Seidel, *J. Pharmacol. Exp. Ther.*, **283**:757-69, 1997.
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Lin *et al.*, *Brain Research*, **591**:319-326, 1992.
20 Opp and Krueger, *American Journal of Physiology* **266**:R688-95, 1994
Panckeri *et al.*, *Sleep*, **19**(8):626-631, 1996.
Seidel, W.F., *et al.*, *J. Pharmacol. Exp. Ther.* **275**:263-273, 1995.
Shelton *et al.*, *Sleep* **18**(10):817-826, 1995.
Welsh, D.K., *et al.*, *Physiol. Behav.* **35**:533-538, 1985.

25 Although the present invention has been described in considerable detail, those skilled in the art will appreciate that numerous changes and modifications may be made to the embodiments and preferred embodiments of the invention and that such changes and modifications may be made without departing from the spirit of the invention. It is therefore intended that the appended claims cover all equivalent variations as fall within 30 the scope of the invention.